

EPA Jacket 11556-150

Vol.1

ISB'S Front-end PRIA Completeness Screen
Draft 3; 10/25/07

EPA Receipt Date: DEC - 3 2009		EPA Reg. Number: 1556-RLN		
	Check List Item	Yes	No	N/A
1	Has the PRIA Fee been Paid; is a copy of the check or Pay.gov receipt included in the Submission Package? 2			
2	Is an Application Form (EPA Form 8570-1) Included in the Submission Package, is it completely filled out and signed including package type?	X		
3	Is a Confidential Statement of Formula (EPA Form 8570-29) Included in the Submission Package, is it completely filled out and signed (boxes 1-21)?	X		
4	Is a Formulator's Exemption Statement (EPA Form 8570-27) Included in the Submission Package?	X		
5	Is a Certification with Respect to Citation of Data (EPA Form 8570-34) Included in the Submission Package?	X		
6	Is a Data Matrix (EPA Form 8570-35) Included in the Submission Package?	X		
7	Is a Label Included in the Submission Package?	X		
8	Are Data Included in the Submission Package?			
9	Is the Submission an Amendment ?			

[illegible]

3

advantage II kitten

For external use only on cats
and kittens 12 weeks and older
and weighing ≥ 5 lbs.

9.10% Imidacloprid
0.45% Pyipresnyfen
Four - 0.0078 fl. oz. (0.23 mL)
EPA Reg. No. 15556-150 83000000, R.1



Rapport B x auf 310,2 mm (bei 32 mm)

Rapport 3 x auf 210 mm

PM No.: 80094337 CR No.: 008376 Format: 210 mm Font size: 6 pt Drawing no.: 9349 Colours: Schwarz Silber	Operator ID AG Member no.: 1 Date 19.07.2010	Bayer Animal Health GmbH approved by BAU-PS-TG/PT Technology on by Text + Layout on by	In case of questions phone: +49 2173 38... Technology: Thomas Fromm Jörg Hübner Uwe Müller Otto Wierfeld Text + Presentation: Christine Müller Rita Felsch Monika Schmitt Renate Schneider
			4702 5519 4814 4701 4724 4068 4062 3046

This proof is NOT a true representation of the final colours that will be printed.

advantage II kitten

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 2 - 5 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

- Kills all flea life stages
- Controls existing flea infestations on your cat and prevents further infestations
- Kills fleas within 12 hours of application
- Convenient, easy-to-apply topical solution
- Fragrance-free
- Waterproof

Active Ingredients	% By Weight
Imidacloprid	9.00%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

See back for First Aid and Precautionary Statements.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

1. Remove one applicator tube from the package. See "HOW TO OPEN" section.
2. Hold applicator tube in an upright position facing away from you and your pet's face and eyes. Pull cap off tube.



3. Turn the cap around and place other end of cap back on tube.
4. Twist cap to break seal, then remove cap from tube.
5. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. Do not get this product in your cat's eyes, or allow your cat to ingest this product. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment.

Treatment at the base of the skull will minimize the opportunity for the cat to lick the product. Do not allow the product to run off.



6. Discard empty tube as described in Storage and Disposal.

7. Under normal conditions this product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four (4) weeks. Do not retreat more often than once every fourteen (14) days. After flea control is attained, return to a monthly retreatment schedule.

PRODUCT INFORMATION

The successive feeding activity of fleas on cats frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage II Kitten kills fleas and may reduce the incidence of this condition.

Advantage II Kitten kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage II Kitten treated cat. Advantage II Kitten provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations.

Advantage II Kitten kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage II Kitten is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

LEO GmbH & Co. KG Postfach 11 33 00919 Düsseldorf Tel. 0211 17 40 40 10 Fax 0211 17 40 40 11	PM no.: 50130165 CR no.: 008378 Format: 145 x 237 mm Font size: 9 pt Drawing no.:	Bayer Animal Health GmbH approved by BAH-PS-TQM/PT Technology	In case of questions phone: +49 2173 38... Technology: Thomas Fromm (T/THF) 4702 Jörg Pabig (T/PAJ) 5818 Uwe Lohrer (T/LOR) 4811 Otto Winkler (T/WKL) 4701	
	Colour: Schwarz Druck:	Drucker: LJI Version: 5 Date: 03.06.2010	Text + Presentation: Christina Hölzer (H/CHZ) 4721 Rita Follmann-Pösch (T/FRP) 4006 Yvonne Stabrich (T/STB) 4292 Renate Strohacker (T/STR) 3048	
	This proof is NOT a true representation of the final colour that will be printed.			



Advantage II - Cat products (11556-150, -151, and -152)

Doug Spilker

to:

Autumn Metzger

10/10/2012 09:12 AM

Cc:

Venus Eagle

Hide Details

From: Doug Spilker <doug.spilker@bayer.com>

To: Autumn Metzger/DC/USEPA/US@EPA

Cc: Venus Eagle/DC/USEPA/US@EPA

History: This message has been replied to.

6 Attachments



Advantage II Kitten jb highlighted.pdf



Advantage II Kitten jb.pdf



Advantage II Large Cat jb highlighted.pdf



Advantage II Large Cat jb.pdf



Advantage II Small Cat jb highlighted.pdf



Advantage II Small Cat jb.pdf

Hi Autumn,

Please find attached the draft master labels (1 clean copy; 1 highlighted copy), text dated 9/25/2012, for the Advantage II Kitten (11556-150), Advantage II Small Cat (11556-151) and Advantage II Large Cat (11556-152). The following are the text changes that were made from the last version. All of the elements of the Final Printed Labeling (facsimile) for these products will be sent under separate emails by product.

Page	Changes to Master label
Page 1	Updated text date to 9/25/12; updated version designation from "ja" to "jb" – see file name.
Page 1	Changed referral statement to show that First Aid appears inside on insert. This was agreed to in email of 8/24/12 (A. Metzger to D. Spilker).

Page 2	First Aid removed, and moved to page 6 (insert).
Page 6-7	Added First Aid section and <i>duplicated</i> Precautionary Statements, Hazards et al. (from page 2) so that it will match the insert of the Final printed labeling.

Please call if you have questions or the labels do not come through correctly.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

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RE: Advantage II Cat Labels (11556-150, -151 and -152)
Doug Spilker to: Autumn Metzger

09/24/2012 12:51 PM

History: This message has been replied to.

Thanks. I never got any stamped labels!?

However, will do. Do I send via email or through the mailroom?

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

From: Autumn Metzger [mailto:Metzger.Autumn@epamail.epa.gov]
Sent: Monday, September 24, 2012 11:48 AM
To: Doug Spilker
Cc: Angela Mall; Venus Eagle
Subject: RE: Advantage II Cat Labels (11556-150, -151 and -152)

Hi Doug,

This is precisely the reason we are asking for the final printed labels. These things have to be worked out to ensure they all fit and match what we stamp. So yes, what you propose is fine, however now we need to start the process over and re-stamp labels. Please re-submit these with no other changes and a very clear cover letter.

Autumn Metzger
Biologist
U.S. Environmental Protection Agency
Insecticide-Rodenticide Branch
Registration Division (7505P)
1200 Pennsylvania Ave. NW
Washington, DC 20460

Tel: 703 305-5314
Fax: 703 308-5433
Email: metzger.autumn@epa.gov

-----Doug Spilker <doug.spilker@bayer.com> wrote: -----

To: Autumn Metzger/DC/USEPA/US@EPA

From: Doug Spilker <doug.spilker@bayer.com>

Date: 09/24/2012 11:24AM

Cc: Angela Mall <angela.strauss@bayer.com>, Venus Eagle/DC/USEPA/US@EPA

Subject: RE: Advantage II Cat Labels (11556-150, -151 and -152)

Good Morning Autumn,

They are working on these package labels to try and meet your deadline. However, they are having trouble fitting all of the new information on the back panel - e.g. new Restrictions section, side effects et al. We would like your permission to move the First Aid section to the insert (and of course change the referral statement to reflect this.) The Precautionary Statements (Hazard to Humans, Hazard to Domestic Animals, Side Effects, and Restrictions would appear on the back panel.) ALL of this information would also be repeated in its entirety on the insert, so the insert is very complete - including all the proper positioning of the First Aid statements with the Precautionary statements.

As I read the LRM (7-10), it says that the Agency may permit reasonable variations in placement of the First Aid statements as long as the referral statement appears on the front panel. We feel this is a reasonable request, and does not increase any potential hazard in using the product.

We ask for your permission to do this. If you need revised Master labels to reflect this change, please let me know and we will fix it.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

From: Autumn Metzger [mailto:Metzger.Autumn@epamail.epa.gov]
Sent: Tuesday, September 18, 2012 2:03 PM
To: Doug Spilker
Subject: Re: Advantage II Cat Labels (11556-150, -151 and -152)

Hi Doug,

These all look ok. Please go ahead and use these to update the final printed labeling for each and submit

to me via email (if possible). We cannot close these out without that part (since I have to be sure the font sizes/colors/pictures and everything else are adequately translated to the final printed labeling). Can we shoot for this back to me within 3 weeks? We'll have to have this closed out before we can finish up the ferret amendment and we would rather not push that back.

Autumn Metzger
Biologist
U.S. Environmental Protection Agency
Insecticide-Rodenticide Branch
Registration Division (7505P)
1200 Pennsylvania Ave. NW
Washington, DC 20460

Tel: 703 305-5314
Fax: 703 308-5433
Email: metzger.autumn@epa.gov

" Doug Spilker ---09/07/2012 07:47:47 AM---Hi Autumn, Here's your welcome back present. Attached are the revised labels for the cat products wi

From: Doug Spilker <doug.spilker@bayer.com>
To: Autumn Metzger/DC/USEPA/US@EPA
Cc: Venus Eagle/DC/USEPA/US@EPA
Date: 09/07/2012 07:47 AM
Subject: Advantage II Cat Labels (tt556-150, -t5 t and -152)

Hi Autumn,
Here's your welcome back present. Attached are the revised labels for the cat products with the changes you requested. I have looked at these ad nauseam, and I hope I fixed everything. The Advantage II dog labels will be in a separate email. I am in the office next week on Monday, and Friday, but in DC Tuesday thru Thursday. I'm hoping we don't, but let me know if we need to work on these some more.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

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(See attached file: Advantage II Kitten ja.pdf)(See attached file: Advantage II Small Cat ja.pdf)(See attached file: Advantage II Large Cat ja.pdf)

DATA PACKAGE BEAN SHEET

Date: 03-Oct-2012

Page 1 of 1

Decision #: 463818

DP #: (405724)

NON PRIA

Parent DP #:

Submission #: 924810

E-Sub #:

*** Registration Information ***

Registration: 11556-150 - ADVANTAGE II KITTEN

Company: 11556 - BAYER HEALTHCARE LLC

Risk Manager: RM 01 - Venus Eagle - (703) 308-8045 Room# PY1 S-7913

Risk Manager Reviewer: Autumn Metzger AMETZGER

Sent Date:

PRIA Due Date: 06-Dec-2012

Edited Due Date:

Type of Registration: Product Registration - Section 3

Action Desc: (300) LABEL REVISION; NO DATA REQUIRED;

Ingredients: 129032, Pyriproxyfen(.48%)

129099, Imidacloprid(9.1%)

*** Data Package Information ***

Expedite: ☐ Yes ☒ No

Date Sent: 03-Oct-2012

Due Back:

DP Ingredient: 129099, Imidacloprid

129032, Pyriproxyfen

DP Title: Companion Animal lowest Weight check

CSF Included: ☐ Yes ☒ No

Label Included: ☐ Yes ☒ No

Parent DP #:

Assigned To

Date In

Date Out

Organization: RD / TRB

Last Possible Science Due Date: 20-10-2012

Team Name: TOX

Science Due Date:

Reviewer Name:

Sub Data Package Due Date:

Contractor Name:

*** Studies Sent for Review ***

No Studies

*** Additional Data Package for this Decision ***

No Additional Data Packages

*** Data Package Instructions ***

Byron:

Please check the original CA studies for this product and verify the lowest weight allowed for the spot-on mitigation.

Thanks,
autumn

300
#31230

OCT 24, 2012

pls type up
1-2 sentences
sol can
give to co!
thank!



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION
OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

October 12, 2012

MEMORANDUM: Minimum Treatment Weight and Age for EPA Reg. No. 11556-150

Subject: Name of Pesticide Product: ADVANTAGE II KITTEN
EPA Reg. No. /File Symbol: 11556-150
DP Barcode: DP 405724
Decision No.: 463818
Action Code: 300
PC Codes: 129099 (Imidacloprid: 9.1%)
129032 (Pyriproxyfen: 0.46%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
Oct - 12 - 2012
Lead Toxicologist

To: Autumn Metzger/Venus Eagle RM 01
Insecticide-Rodenticide Branch
Registration Division (7505P)

Registrant: BAYER HEALTHCARE LLC

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>	by wt.
129099 Imidacloprid	9.10%
129032 Pyriproxyfen	0.46%
<u>Other Ingredient(s):</u>	90.44%
TOTAL	100.00%

ACTION REQUESTED: The Risk Manager requests:

"...Please check the original companion animal studies for this product and verify the lowest weight allowed for the spot-on mitigation..."

BACKGROUND:

The companion animal safety studies that supported the registration of EPA Reg. No. 11556-150 are an adult cat study in MRID 45097001 (Abraham, A. (2000) Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation in the Target Species, Adult Cats: Lab Project Number: 75122. Unpublished study prepared by Bayer Corporation. 139 p. {OPPTS 870.7200}) and a kitten study in MRID 47924801 (Madsen, T. (2009) Evaluation of the General Safety of M880. Project Number: 152/141, S07648, 33714. Unpublished study prepared by Sinclair Research Center, Inc. 193 p.). The last accepted (September 27, 2010) label indicates that this product (packaged in tubes containing 0.0078 fl. oz. or 0.23 mL formulation) is for once-a-month topical treatment for fleas and lice on cats and kittens 8 weeks and older and weighing under 5 lbs.

COMMENTS AND RECOMMENDATIONS:

1. In the cited adult cat study (MRID 45097001) Day -1 weights of the treated (5X) cats ranged from 5.23 to 10.9 lbs. Cats weighing up to 9 lbs were dosed with 2 mL (5 x 0.4 mL), while cats weighing more than 9 lbs were dosed with 4.0 mL (5 x 0.8 mL). The cats were treated at weekly intervals (Days 0, 7, 14 and 21). The statement is made (p. 17 of MRID 45097001) that: "This resulted in a 20X the monthly use volume applied in a months time." However, TRB concludes that this study (by itself) could only be used to set a minimum weight that would be greater than 5 lbs.
2. The following are excerpts from the executive summary of the review (TXR 5012077; EPA File Symbol: 11556-RLN, memorandum dated April 15, 2010) of the companion animal (kitten) safety study in MRID 47924801:

In a companion animal safety study (MRID 47924801), 5 groups, each containing 6 males and 6 females, of domestic shorthair kittens (54-57 days old on Day 0; Day -1 body weights: males: 0.691-1.012 kg; females: 0.555-0.935 kg; source: Liberty Research, Inc., Waverly, NY), were topically treated (on Day 0) with (Group 1): mineral oil at a total dose of 1.15 mL; (Group 2): 3X vehicle substance at a total dose of 0.63 mL; (Group 3): 5X vehicle substance at a total dose of 1.05 mL; (Group 4): 3X test substance at a total dose of 0.69 mL; and (Group 5): 5X dose test substance at a total dose of 1.15 mL. For each group, the total dose was split into three sub-applications which were administered at approximately 60-minute intervals. The application site was the skin on the dorsal midline from the base of the skull to the interscapular region. The dosing was repeated on Day 14.

The groups and test materials they received (with amounts applied) are shown in the table below:

Group	Test Material Applied	Volume of each application	Cumulative amount applied on Day 0; also on Day 14
1	Mineral oil	1 st app = 0.35 mL; 2 nd & 3 rd = 0.4 mL	1.15 mL
2	Vehicle of proposed formulation (no active ingredients) at 3X	3 applications @ 0.21 mL	0.63 mL
3	Vehicle of proposed formulation (no active ingredients) at 5X	3 applications @ 0.35 mL	1.05 mL
4	Proposed formulation (with active ingredients) at 3X	3 applications @ 0.23 mL	0.69 mL
5	Proposed formulation (with active ingredients) at 5x	1 st app = 0.35 mL; 2 nd & 3 rd = 0.4 mL	1.15 mL

...Body weights were determined on days -7, -3, -1, 1, 15 and 28. Physical examinations were conducted by a veterinarian on days -7, -3, 1, 15 and 28...

All animals survived to the end of the study...

One Group 5 male (08KPK1) was lethargic on day 15 (the day following the second dosage). This was the only reported occurrence of lethargy in the study; also it was the only kitten in this group with coat effects on day 15; this animal had shown diarrhea on day 14 pre-dose and on day 15. The overall mean food consumption of this animal (49.4 g/day) from week 1 to 4 was lower than values of the other males (range: 52.9 to 69.0 g/day) in this group, and was particularly low (36.6 g/day) during week 2 (presumably from day 7 through 13, a period that did not include an application of the test material). According to the report summary this kitten demonstrated intermittent anorexia (days 11 and 15) resulting in mild weight loss and transient dehydration and lethargy, with immediate improvements in food consumption and general condition noted following supplementation of the diet with moist food.

All kittens gained weight from Day -1 to Day 28. Mean body weight gains of Group 5 (5X test material) males and females were noticeably lower than those of the other groups in the period from Day -1 to Day 20 (which included applications on Days 0 and 14). Group 5 males had a weight gain that was 87% of that for Group 1 males, and Group 5 females had a value that was 92.6% that of Group 1 females. Group 4 (3X test material) males and females had values slightly greater than those of their Group 1 counterparts.

It is concluded that the margin of safety in kittens administered a topical application of the product formulation is at least 3X. Possible effects observed at 5X included lethargy in one male kitten following the second set of applications, and decreased body weight gains in both males and females in the period from day -1 to day 20. As noted in the current 870.7200 Guidelines: "Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-threatening signs)."

This companion animal safety study in male and female domestic shorthair kittens is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in 54-57 day (8 week) kittens.

3. From page 89 of MRID 47924801, on Day -1 the individual weights of the male kittens in Group 4 (3X) ranged from 0.761 to 0.888 kg (1.678-1.958 lb), while the male kittens in Group 5 (5X) ranged from 0.777 to 1.012 kg (1.713-2.231 lb). The respective means with standard deviations were [3X] 0.825 ± 0.053 and [5X] 0.863 ± 0.090 kg (1.818 ± 0.117 and 1.903 ± 0.199 lbs, respectively). From data on page 90, on Day -1 the individual weights of the female kittens in Group 4 (3X) ranged from 0.637 to 0.820 kg (1.404 to 1.808 lbs) while the female kittens in Group 5 (5X) ranged from 0.613 to 1.112 kg (1.351 to 2.452 lbs). The respective means with standard deviations were [3X] 0.731 ± 0.070 and [5X] 0.772 ± 0.103 kg (1.611 ± 0.153 and 1.703 ± 0.227 lbs, respectively). The mean weight for all kittens in Group 4 was 0.778 kg (1.715 lbs) and for all kittens in Group 5 was 0.818 kg (1.803 lbs).
4. Based on the weights of the treated kittens in this study, and taking into account that a 3X (rather than 5X) margin of safety was established, **we can accept 2 lbs as the minimum weight.**
5. As noted in the executive summary given above, the ages of the kittens on the day of first dosing ranged from 54 to 57 days. **We can accept 8 weeks as the minimum age.**

FAST-TRACK AMENDMENTS – Completeness Screening Checklist

Expert's In-Processing Signature: E. Fatul Date: 4/12/12 PM #: 1

EPA Reg. Number: <u>11556-150</u>		EPA Receipt Date: <u>4/11/12</u>		
	Checklist Item	Yes	No	N/A
1	Application Form (EPA Form 8570-1) - signed?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Confidential Statement of Formula (EPA Form 8570-29) - signed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
3	Certification with Respect to Citation of Data (EPA Form 8570-34) - signed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
4	Formulator's Exemption Statement (EPA Form 8570-27) - signed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
5	Data Matrix (EPA Form 8570-35) [Applicable for adding me-too uses] - signed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	a) Selective Method?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	b) Cite-All Method?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	c) Public copy of Matrix provided? See PR Notice 98-5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	Is Label included? (5 copies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	a) Electronic Label available?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Comments: 				

Receipt for Section 3

S: 815114

Resubmission: ☐ Yes ☒ No

Regulatory Type: Product Registration - Section 3

Fee For Service: ☐ Yes ☒ No

Application Type: Amendment

Billable: ☐ Yes ☒ No

Company: 11555 BAYER HEALTHCARE LLC

V

Risk Manager: Registration Division, Risk Management Team 1

Product #: 11555-150

Product Name: ADVANTAGE I KITTEN

Overmold:

Me Too Section 3:

Me Too Product Name:

Application Date: 09-Apr-2012

OPP Rec'd Date: 11-Apr-2012

Front End Date: 11-Apr-2012

Risk Manager Send Date: 12-Apr-2012

FPS Due Date:

Negotiated Due Date:

OPP Target Date:

Fast Track: ☐

New Ingredient: ☐

Receipt Description:

Label amendment

Form A: ☐

Signature Date:

Form B: ☐

Signature Date:

New Ingredient Request Date:

New Ingredient Received Date:

Print Letter

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Tracking

Receipt Content

Paper Label

View/Edit



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

April 12, 2012

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DR. BRUCE MARTIN
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

PRODUCT NAME: ADVANTAGE II KITTEN
COMPANY NAME: BAYER HEALTHCARE LLC
OPP IDENTIFICATION NUMBER:
EPA FILE SYMBOL: 11556-150
EPA RECEIPT DATE: 04/11/12

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application appears to qualify for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability for fast track status.

If you have any questions, please contact Registration Division, Risk Management Team 1, at (703) 308-8045.

Sincerely,

A. K. Moore
Front End Processing Staff
Information Services Branch
Information Technology & Resources Management Division

Fee for Service

{915114v~

This package includes the following

- ☐ New Registration
- ☒ Amendment

☐ Studies? ☐ Fee Waiver?

☐ volpay % Reduction: ____

for Division

- ☐ AD
- ☐ BPPD
- ☒ RD

Risk Mgr. 1

Receipt No.

S-

915114

EPA File Symbol/Reg. No.

11556-150

Pin-Punch Date:

4/11/2012



This item is NOT subject to FFS action.

Action Code:

Requested:

Granted:

Amount Due: \$ _____

Parent/Child Decisions:

☒ Inert Cleared for Intended Use

☐ Uncleared Inert in Product

Reviewer: *[Signature]*

Date: 4/12/12

Remarks:

Bayer HealthCare
Animal Health



Via Federal Express

April 9, 2012

Document Processing Desk (AMEND- Pet Spot-on)
Office of Pesticide Programs (7505P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM 01

Subject: Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Ms. Eagle:

Reference is made to the current registrations of the subject products, and the Agency's letter to us, dated September 20, 2011 (received October 11, 2011), regarding "Implementation of Label Changes to Pet Spot-on Products."

Please find enclosed for the Agency's review and acceptance respective applications and revised draft labeling, dated 03/26/2012, for each of the subject dog spot-on products. Many of the revisions are in response to the aforementioned EPA "Implementation" letter, but we have also taken the opportunity in these amendments to make a few minor word and format changes. However, there have been no revisions of any efficacy claims.

The letter from the Agency requests the submission of "packaging" of these products. In addition to the enclosed "Master" labels for the products, we have also enclosed one copy of the printer's proofs of each element of the Final Printed Labeling (packaging) for these products.

Since the mandated label revisions outlined in the aforementioned Agency letter affect all pet spot-on pet registrations, we encourage the Agency to issue a PR Notice, or other regulatory document, that will also mandate a single date of packaging compliance for the entire affected industry as one. If you have any questions, please do not hesitate to call (913-268-2751).


Sincerely,



Douglas A. Spilker, Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker@Bayer.com

Enclosures:

- 1) Advantage II Kitten - Application w/att.
- 2) Advantage II Kitten - Draft label, dated 3/26/12 (3 copies)
- 3) Advantage II Kitten - Final printed labeling proofs (1 copy)
- 4) Advantage II Small Cat - Application w/att.
- 5) Advantage II Small Cat - Draft label, dated 3/26/12 (3 copies)
- 6) Advantage II Small Cat - Final printed labeling proofs (1 copy)
- 7) Advantage II Large Cat - Application w/att.
- 8) Advantage II Large Cat - Draft label, dated 3/26/12 (3 copies)
- 9) Advantage II Large Cat - Final printed labeling proofs (1 copy)

 EPA United States Environmental Protection Agency Washington, DC 20460	<input type="checkbox"/> Registration <input checked="" type="checkbox"/> Amendment <input type="checkbox"/> Other:	OPP Identifier Number
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Application for Pesticide - Section I

1. Company/Product Number 11556-150	2. EPA Product Manager Venus Eagle	3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted
4. Company/Product (Name) Advantage II Kitten	PM# 1	
5. Name and Address of Applicant (Include ZIP Code) Bayer HealthCare LLC, Animal Health Division PO Box 390 Shawnee Mission, KS 66201		6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____

☐ Check if this is a new address
Section - II

<input checked="" type="checkbox"/> Amendment - Explain below. <input type="checkbox"/> Resubmission in response to Agency letter dated _____ <input type="checkbox"/> Notification - Explain below.	<input type="checkbox"/> Final printed labels in response to Agency letter dated _____ <input type="checkbox"/> "Me Too" Application <input type="checkbox"/> Other - Explain below
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Explanation:

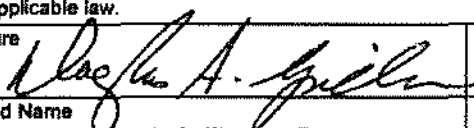
NON-PRIA ACTION (AMEND - Pet Spot-on). See attached for more detail.

Enclosed for Agency acceptance is revised draft labeling for the subject product, dated 03/26/12. Revisions include those in response to the EPA "Implementation of Label Changes to Pet Spot-On Products" document, dated 9/30/11 (Received 10/11/11), and other minor word and format changes. Final Printed Labeling for this product is also enclosed.

Section - III

1. Material This Product Will Be Packaged In:				2. Type of Container	
Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No	Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No	Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No		<input checked="" type="checkbox"/> Metal	
	If "Yes" Unit Packaging wgt.	No. per container	If "Yes" Package wgt.	No. per container	<input type="checkbox"/> Plastic
*Certification must be submitted					<input type="checkbox"/> Glass
					<input type="checkbox"/> Paper
					<input type="checkbox"/> Other (Specify)
3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container	4. Size(s) Retail Container		5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On labeling accompanying product		
6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled		<input type="checkbox"/> Other _____			

Section - IV

1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application)					
Name Douglas A. Spilker, Ph.D.		Title Manager, EPA Regulatory Affairs		Telephone No. (Include Area Code) 913-268-2751	
Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.					6. Date Application Received (Stamped)
2. Signature 		3. Title Manager, EPA Regulatory Affairs			
4. Typed Name Douglas A. Spilker, Ph.D. (doug.spilker@bayer.com)		5. Date 9 April 2012			

ATTACHMENT FOR
APPLICATION FOR PESTICIDE REGISTRATION

April 5, 2012

Advantage II Kitten (EPA Reg. No. 11556-150)

Please find enclosed for the Agency's review and acceptance revised draft labeling, dated 03/26/12, for the subject product. Many of the revisions are in response to the EPA "Implementation of Label Changes to Pet Spot-On Products" document, dated 9/30/11 (Received 10/11/11), but we have also taken the opportunity in this amendment to make a few minor word and format changes. However, there have been no revisions of any efficacy claims. Also, enclosed is the Final Printed Labeling for this product, as requested in the aforementioned EPA document.

The proposed changes to the draft labeling are:

Page 1:

1. Revision of the weight and age restriction statement, with a box surrounding it. The minimum weight was determined from the EPA-accepted Companion Animal Safety studies for this product.
2. Slight revision of the referral statements.

Page 2:

3. In the "HAZARDS TO DOMESTIC ANIMALS," addition of the minimum weight for the kittens.
4. Addition of "Side Effects" text in a box; basically the "boiler plate" language specified by the Agency in the aforementioned document, with slight product-specific modifications, based on the findings in the EPA-accepted Companion Animal Safety studies for this product, and from accident reports from cases of properly applied product.
5. Addition of 1-800 numbers for carton.

Page 3:

6. Addition of the minimum weight restriction to bullet #1 of the "HOW TO APPLY" section.

Page 4:

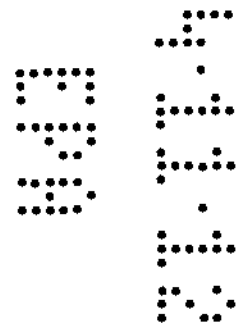
7. Incorporation of the required "do not allow your cat to ingest this product" statement into the language of the bullet #6 of the draft label.

Pages 5-9:

- No changes.

No other substantive changes have been made to this label, except for those listed above. Therefore, we hope that these minor changes to the label can be readily accepted by the Agency for this product, as well as, for the revised label of the other Advantage cat products – Advantage II Small Cat & Advantage II Large Cat - submitted concurrently with this application.

If there are any questions regarding these revisions, please contact us immediately [doug.spilker@bayer.com ; (913)-268-2751].



Bayer HealthCare
Animal Health



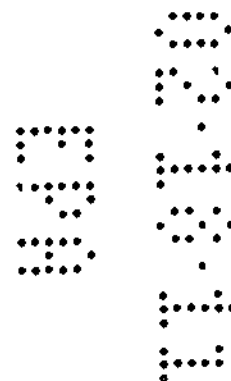
Via Federal Express 02/17/2011

**Document Processing Desk (Final Printed Labeling)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501**

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Enclosure: Application for Pesticide (other) – Final Printed Labeling (2 copies each)

Advantage II Kitten (EPA No. 11556-150) (83000490, R.0)
Advantage II Small Cat (EPA No. 11556-151) (04461669, R.0)
Advantage II Large Cat (EPA No. 11556-152) (0461685, R.0)





United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☒ Other

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number 11556-150	2. EPA Product Manager Venus Eagle	3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted
4. Company/Product (Name) Advantage II Kitten	PM# 01	
5. Name and Address of Applicant (Include ZIP Code) Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390 <input type="checkbox"/> Check if this is a new address	6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: <input checked="" type="checkbox"/> EPA Reg. No. _____ Product Name _____	

Section - II

<input type="checkbox"/> Amendment - Explain below.	<input checked="" type="checkbox"/> Final printed labels in response to Agency letter dated JUN 24 2010
<input type="checkbox"/> Resubmission in response to Agency letter dated _____	<input type="checkbox"/> "Me Too" Application.
<input checked="" type="checkbox"/> Notification - Explain below.	<input type="checkbox"/> Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Submission of Final Printed Labeling - No action required.

Contact: doug.spilker@bayer.com

Section - III

1. Material This Product Will Be Packaged In:				2. Type of Container	
Child-Resistant Packaging <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Unit Packaging <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Water Soluble Packaging <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		<input checked="" type="checkbox"/> Metal	<input type="checkbox"/> Plastic
* Certification must be submitted				<input type="checkbox"/> Glass	<input checked="" type="checkbox"/> Paper
	If "Yes" Unit Packaging wgt. No. per container	If "Yes" Package wgt. No. per container		Other (Specify) _____	
3. Location of Net Contents Information <input type="checkbox"/> Label <input checked="" type="checkbox"/> Container		4. Size(s) Retail Container 4-0.23ml tube	5. Location of Label Directions <input type="checkbox"/> On Label <input checked="" type="checkbox"/> On Labeling accompanying product		
6. Manner in Which Label is Affixed to Product <input checked="" type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled		<input type="checkbox"/> Other _____			

Section - IV

1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)		
Name Douglas A. Spilker, Ph D.	Title EPA Reg. Affairs Manager	Telephone No. (include Area Code) 913-268-2751
Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.		6. Date Application Received (Stamped)
2. Signature 	3. Title EPA Reg. Affairs Manager	
4. Typed Name Douglas A. Spilker, Ph D.	5. Date 2/17/2011	



advantage® II

kitten

Once-A-Month Topical Flea Prevention and Treatment for Cats

For Use ONLY on Cats 8 Weeks and Older

For Use ONLY on Cats Weighing Under 5 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE.

For the Prevention and Treatment of Flea Infestations

- Kills all flea life stages
- Controls existing flea infestations on your cat and prevents further infestations
- Kills fleas within 12 hours of application
- Convenient, easy-to-apply topical solution
- Fragrance-free
- Waterproof

Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See back for First Aid and Precautionary Statements.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

1. Use only on cats and kittens. Do not use on other animals.
2. Remove one applicator tube from the package. See "HOW TO OPEN" section.
3. Hold applicator tube in an upright position. Pull cap off tube.



4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.



6. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. *Do not get this product in your cat's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment.* Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.

7. Discard empty tube as described in Storage and Disposal.

8. Under normal conditions the product is effective for a month. However, in cases of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not retreat more often than once every fourteen (14) days. After flea control is attained, return to a monthly retreatment schedule.

ADDITIONAL INFORMATION

The successive feeding activity of fleas on cats frequently may elicit a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage II Kitten rapidly kills fleas and reduces the incidence of this condition.

Advantage II Kitten kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage II Kitten treated cat. Advantage II Kitten provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage II Kitten kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage II Kitten is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

KEEP OUT OF REACH OF CHILDREN

CAUTION

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on kittens under 8 weeks of age. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats.

If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product. If your cat is experiencing an adverse event, contact your veterinarian and, call 1-800-422-9874.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place.
Pesticide Disposal and Container Handling: Nonrefillable container.

If empty: Do not reuse this container. Place in trash or offer for recycling if available.

If partly filled: Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

FIRST AID	
If Swallowed:	<ul style="list-style-type: none">• Call a poison control center or doctor immediately for treatment advice.• Have person sip a glass of water if able to swallow.• Do not induce vomiting unless told to do so by the poison control center or doctor.• Do not give anything to an unconscious person.
If In Eyes:	<ul style="list-style-type: none">• Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.• Call a poison control center or doctor for treatment advice.
If On Skin:	<ul style="list-style-type: none">• Wash with plenty of soap and water.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For medical emergencies call 1-800-422-9874. For customer questions call 1-800-255-6826.	
NOTE TO PHYSICIAN	
Treat the patient symptomatically.	

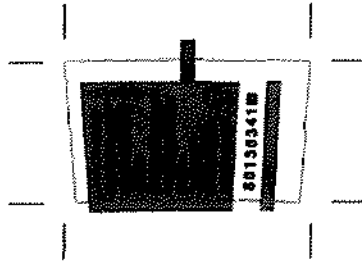
Manufactured For
Bayer HealthCare LLC, Animal Health Division,
P.O. Box 390, Shawnee Mission, Kansas 66201 USA
Bayer, the Bayer Cross and Advantage are
registered trademarks of Bayer
© 2010 Bayer HealthCare LLC
Made in Germany

Advantage II is protected by the following U.S.
patents: 6,232,328 and 6,001,858

80130198
83000512/83000490, R.O
EPA Est. No. 11556-DEU-1
EPA Reg. No. 11556-150

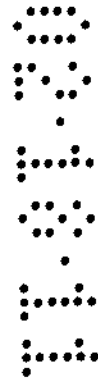


Bayer HealthCare



PM no.: 80130341 CR no.: 008378 Format: 20,5 x 35 mm Font size: 8 pt Drawing no.: 6101E	Bayer Animal Health GmbH approved by BAH-PS-TO/PPT Technology	In case of questions phone: +49 2173 38... Technology: Thomas Fromm (VDFD) 4702 Jörg Hübner (TGS-AL) 5518 Uwe Müller (TGS-AL) 4514 Otto Wernold (VTWL) 4701 Text + Presentations: Christina Hübner (HUNO) 4724 Rita Felchus Reich (VREB) 4538 Yvonne Saberski (TGT-VO) 4582 Hanna Stenacker (VSTIE) 3049
Colours: Schwarz Pantone 306 Blau	on by Text + Layout on by	
Date: 22.07.2010		

This proof is NOT a true representation of the final colours that will be printed.



80130252


advantage II
 Kitten

 8 Weeks and Older
 and Under 5 lbs.

4

4
Over
5 lbs

advantage II
 kitten


advantage II
 Kitten


advantage II

kitten

Once-a-Month Topical Fleas Prevention and Treatment for Cats
 For Use ONLY on Cats 8 Weeks and Older
 For Use ONLY on Cats Weighing Under 5 lbs.

- Kills all flea life stages
- Controls existing flea infestations on your cat and prevents further infestations
- Kills fleas within 12 hours of application

Active Ingredients	% By Weight
Imidacloprid	5.16%
Pyrimethanil	0.46%
Other Ingredients	94.38%
Total	100.00%

Net Contents: 0.14 fl. oz. (4.0 mL)

KEEP OUT OF REACH OF CHILDREN
CAUTION

 See back panel for first aid.
 For directions for use, and storage and
 disposal, see supplementary labeling inside.


24089-00490

4

Lot No.:


advantage II
Once-a-Month Topical Fleas Prevention and Treatment for Cats
 For Use ONLY on Cats 8 Weeks and Older
 For Use ONLY on Cats Weighing Under 5 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE
 For the Prevention and Treatment of Flea Infestations
 3-way flea protection: kills adults, larvae and eggs.
 Controls existing flea infestations on your cat and
 prevents further infestations.
 Also kills within 12 hours of application.

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS
 Irritant if swallowed. Causes moderate eye irritation.
 Avoid contact with eyes or clothing. Wash hands
 thoroughly with soap and warm water after handling.
 Keep out of reach of children. Do not inhale dust or
 fumes.

HAZARDS TO DOMESTIC ANIMALS
 For adult cats only. Do not use on kittens under 8
 weeks of age. As with any product, consult your
 veterinarian before using this product on debilitated,
 aged, pregnant or nursing cats. Individual
 reactions, while rare, may occur after using ANY
 pesticide product for cats. If signs persist, or become
 more severe, consult a veterinarian immediately. If
 your cat is on medication, consult your veterinarian
 before using this or any other product.
 If your cat is experiencing an adverse event, consult
 your veterinarian, and call 1-800-435-9575.

KEEP OUT OF REACH OF CHILDREN
 It is a violation of Federal Law to use this product in a
 manner inconsistent with its labeling.

HOW TO APPLY
 1. Being careful not to get close to the animal's ear, use
 the applicator and cut off one section of the card
 containing a single tube.

 2. Gently squeeze tube as described in Storage and
 Disposal.

 3. Under normal conditions the product is effective
 for a month. However, in cases of severe flea
 infestation, reapplication may be necessary earlier
 than five weeks. Do not reapply more often than
 once every fourteen (14) days. After flea control is
 obtained, return to 1 monthly reapplication schedule.

 4. Do not get this product in your cat's eyes or mouth.
 The product is better feeling and
 soothing than many flea treatments.
 Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 5. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 6. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 7. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 8. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 9. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 10. Do not use this product on cats with open wounds.
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 11. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
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 12. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
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 13. Do not use this product on cats with open wounds.
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 14. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 15. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
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 16. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
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 17. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 18. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 19. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 20. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 2. Take the separated section, and cut into the skin
 evenly across the small side. Close to the cap of the
 tube.

3. Peel off the lid, and take out the tube.

4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY
 1. Use only on cats and kittens. Do not use on other
 animals.

 2. Remove one applicator tube from the package. See
 "HOW TO OPEN" section.

 3. Hold applicator tube in an upright position. Pull cap
 off tube.

 4. Turn the cap around and place other end of cap back
 on tube.

5. Push cap to break seal, then remove cap from tube.



 6. Put the bulk of the tube at the base of the skull
 with the side to which. Place the tip of the tube on
 the skin and squeeze the tube to expel the white
 contents directly on the skin.

 Do not get this product in your cat's eyes or mouth.
 The product is better feeling and
 soothing than many flea treatments.
 Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 7. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 8. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

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 Treatment at the base of the skull will maintain the
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 opportunity for the cat to lick the product.

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 Treatment at the base of the skull will maintain the
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 opportunity for the cat to lick the product.

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 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 15. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 16. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 17. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 18. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 19. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 20. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 21. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.

 22. Do not use this product on cats with open wounds.
 Treatment at the base of the skull will maintain the
 opportunity for the cat to lick the product.



advantage® II

kitten

Once-A-Month Topical Flea Prevention and Treatment for Cats

For Use ONLY on Cats 8 Weeks and Older

For Use ONLY on Cats Weighing Under 5 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE.

For the Prevention and Treatment of Flea Infestations

- Kills all flea life stages
- Controls existing flea infestations on your cat and prevents further infestations
- Kills fleas within 12 hours of application
- Convenient, easy-to-apply topical solution
- Fragrance-free
- Waterproof

Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See back for First Aid and Precautionary Statements.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

1. Use only on cats and kittens. Do not use on other animals.
2. Remove one applicator tube from the package. See "HOW TO OPEN" section.
3. Hold applicator tube in an upright position. Pull cap off tube.



4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.



6. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. *Do not get this product in your cat's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment.* Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.

7. Discard empty tube as described in Storage and Disposal.

8. Under normal conditions the product is effective for a month. However, in cases of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not retreat more often than once every fourteen (14) days. After flea control is attained, return to a monthly retreatment schedule.

ADDITIONAL INFORMATION

The successive feeding activity of fleas on cats frequently may elicit a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage II Kitten rapidly kills fleas and reduces the incidence of this condition.

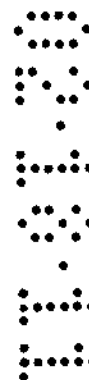
Advantage II Kitten kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage II Kitten treated cat. Advantage II Kitten provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage II Kitten kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage II Kitten is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.



KEEP OUT OF REACH OF CHILDREN

CAUTION

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on kittens under 8 weeks of age. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats.

If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product. If your cat is experiencing an adverse event, contact your veterinarian and, call 1-800-422-9874.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place.

Pesticide Disposal and Container Handling: Nonrefillable container.

If empty: Do not reuse this container. Place in trash or offer for recycling if available.

If partly filled: Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

FIRST AID	
If Swallowed:	<ul style="list-style-type: none">• Call a poison control center or doctor immediately for treatment advice.• Have person sip a glass of water if able to swallow.• Do not induce vomiting unless told to do so by the poison control center or doctor.• Do not give anything to an unconscious person.
If In Eyes:	<ul style="list-style-type: none">• Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.• Call a poison control center or doctor for treatment advice.
If On Skin	<ul style="list-style-type: none">• Wash with plenty of soap and water.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For medical emergencies call 1-800-422-9874. For customer questions call 1-800-255-6826.	
NOTE TO PHYSICIAN	
Treat the patient symptomatically.	

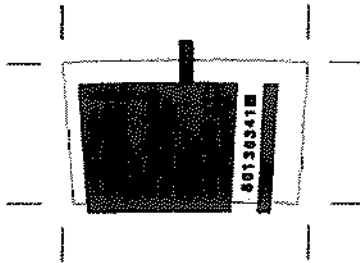
Manufactured For
Bayer HealthCare LLC, Animal Health Division,
P.O. Box 390, Shawnee Mission, Kansas 66201 USA
Bayer, the Bayer Cross and Advantage are
registered trademarks of Bayer
© 2010 Bayer HealthCare LLC
Made in Germany

80130198
83000512/83000490, R.0
EPA Est. No. 11556-DEU-1
EPA Reg. No. 11556-150

Advantage II is protected by the following U.S.
patents: 6,232,328 and 6,001,858

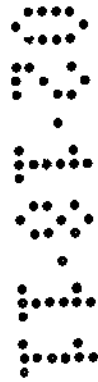


Bayer HealthCare



P/N no.: 60130341 CR no.: 008376 Format: 20.5 x 35 mm Font size: 8 pt Drawing no.: 6101E Colour: Schwarz Pen: 325 Size: 2 Date: 22.07.2010	Bayer Animal Health GmbH approved by BAH-PS-TO/PT Technology on by Text & Layout on by	In case of questions phone: +49 2173 38... Technology: Thomas Fromm (VTR) 4702 Jörg Hübner (TGA) 5519 Uwe Müller (TGA) 4814 Otto Wilm (VTR) 4701 Text & Presentations: Christina Höber (FJUNG) 4724 Rita Felicitas Reich (VTR) 4098 Yvonne Sauer (TGV) 4082 Renate Stehner (VTR) 3046
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This proof is NOT a true representation of the final colours that will be printed.



Bayer HealthCare
Animal Health



June 01, 2011

Document Processing Desk
Office of Pesticide Programs (7504P) – NonPR1A
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM01

Subject: Advantage II Kitten (EPA Reg. No. 11556-150)
 Advantage II Small Cat (EPA Reg. No. 11556-151)
 Advantage II Large Cat (EPA Reg. No. 11556-152)
 Advantage II Small Dog (EPA Reg. No. 11556-128)
 Advantage II Medium Dog (EPA Reg. No. 11556-125)
 Advantage II Large Dog (EPA Reg. No. 11556-127)
 Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201

Bayer HealthCare LLC, Animal Health Division received notice from the Agency for the conditional registration requirement of enhanced quarterly incident reporting for Advantage II Dog and Cat registrations on April 29, 2010 and June 24, 2010 respectively. This enhanced reporting was to begin with the quarter starting January 01, 2011. In compliance with this request, Bayer is providing the following listing of incident reports along with tables of additional analysis as requested in the Agency's letters of April 29, 2010 and June 24, 2010. In addition, Bayer's letters to the Agency regarding notification of first shipment dated December 09, 2010 are attached for reference.

This submission includes the following tables covering incident reporting from January 01, 2011 through March 31, 2011:

Summary Table (multiple pages due to length)
Breed Summary
Age Range Summary
Clinical Signs Summary
Organ System Summary
Patient Weight Range Summary
Product Weight Range Summary



Page 2 of 3

Route of Exposure Summary
Secondary Exposure Summary

Due to the length of some of the tables and to provide the Agency the ability to sort, this data is being provided electronically on a CD. The data was extracted from Bayer's pharmacovigilance data base (P.V. Works).

Deaths

Deaths were reported in two (2) felines that had previously received treatment with Advantage II during the period of review. Specifics are as follows:

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201

2011-US0006708

An unspecified Advantage II product (unknown if for Dogs or Cats and unknown dose) was applied to a 6 year old male cat of unknown weight and breed. An undetermined time post-application, the cat made a low, grumbling sound, his body went limp, and he wasn't moving. The owner took the cat to a veterinarian who was unable to resuscitate the cat. No necropsy examination was performed.

Assessment:

Death would not be expected with topical use of the product. With no necropsy being performed it is impossible to verify cause of death and any involvement the product may have had. The product was applied to other cats in the household at the same time without consequence. The attending veterinarian suspects cardiac arrest of unknown reason and the veterinarian did not believe the event was product-related.

2011-US0007111

On 25 Mar 2011 Advantage II Large Cat was applied to Corduroy an 11 pound, 10 year old, neutered male, Domestic Shorthair per labeled directions. At the same time Advantage II was applied a Capstar was given per the direction of the vet. Capstar and Advantage II were administered to Corduroy due to a massive flea infestation that was causing severe anemia. At an unspecified time after application Corduroy became anorexic, wouldn't drink, was lethargic and ended up passing away on 27 Mar 2011.

Assessment:

Bayer HealthCare
Animal Health



Page 3 of 3

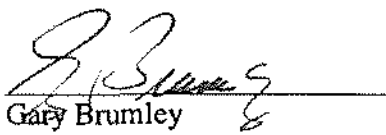
Symptoms leading to death would not be expected with the topically acting product. The patient also had severe anemia which needs to be considered. With out a necropsy being performed it is impossible to verify the cause of death and any involvement the product may have had. What role, if any, the concomitant medications played in this case cannot be determined as well. The owner noted she did not believe that the product played a role in the patient's death.

We believe this summary of data meets the requested information in the Agency's requirements for enhanced reporting as outlined in its January 19, 2011 communication to Bayer.

A report with the confidential sales information and additional analysis of incident rates based on doses sold is being sent to the Registration Division, Immediate Office (attn. Ms. Kimberly Nesci).

If there are any questions regarding this submission, please contact me by phone at 913.268.2573 or by e-mail at gary.brunley@bayer.com.

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201



Gary Brunley
Senior Consultant
Regulatory Affairs

Bayer HealthCare
Animal Health



Via Federal Express - Express Saver

December 9, 2010

Document Processing Desk
Office of Pesticide Programs (7504P) – NonPRIA
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM 01

Subject:

Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)

Dear Ms. Eagle:

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Reference is made to the current registrations of the subject products. One of the conditions of acceptance of the subject registrations is that "[We] must provide the Agency with a projected release for shipment at least 30 days in advance."

Therefore, we are hereby notifying the Agency that our first anticipated shipment of product will be on or after January 17, 2011.

If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely,

A handwritten signature in cursive script, appearing to read "Douglas A. Spilker".

Douglas A. Spilker, Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker@Bayer.com

Cc: K. Davis (EPA) – email

Material to be added to an e-Jacket/Jacket

Reg. No. 11SSG-150

Decision # 440179

Description: Accepted notification

1. Placement within the e-Jacket/jacket:

- ☒ Default: (chronological, top = newest)
☐ File Location: (eg. "before page 45 in .pdf")

2. ☒ Send to Data Extraction contractors this material:

- ☐ Newly stamped accepted label
☒ Notification
☐ New CSF
☐ Other: _____

3. Attach this coversheet to the top of the material or jacket. It must be well organized and clipped together, NOT STAPLED. Then give the material with this coversheet to staff in the Information Services Center (Room S-4900).

Reviewer: Jennifer Urban Division: RD
Phone: 703-347-0156 Date: 9/27/10



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Mary McKinney Hunt
Bayer HealthCare LLC
Animal Health Division
PO Box 390
Shawnee Mission, KS 66201

SEP 27 2010

Subject: Notification of the addition of the EPA Registration Number and the optional text [Sample-not for (re)sale] for Advantage II Kitten (EPA Reg. # 11556-150)

Dear Ms. McKinney Hunt:

The Agency is in receipt of your Application for Pesticide Notification under Pesticide Registration Notice (PRN) 98-10 dated 9/15/2010 for the product Advantage II Kitten (EPA Reg. # 11556-150). The Registration Division (RD) has conducted a review of this request for its applicability under PRN 98-10 and finds that the action(s) requested fall within the scope of PRN 98-10. The Confidential Statement of Formula (CSF) and/or label submitted with the application has (have) been stamped "Notification" and will be placed in our records.

If you have any questions, please call me directly at 703-347-0156 or urbanski.jennifer@epa.gov.

Sincerely,

A handwritten signature in black ink, appearing to read "J. Urbanski".

Jennifer Urbanski
Registration Division (7505P)
Office of Pesticide Programs

**EPA**

United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☒ Other:

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number 11556-150	2. EPA Product Manager Venus Eagle	3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted
4. Company/Product (Name) Advantage II Kitten	PM# 01/Team 1	
5. Name and Address of Applicant (include ZIP Code) Bayer HealthCare LLC, Animal Health Division PO Box 390 Shawnee Mission, KS 66201	6. Expedited Review. in accordance with FIFRA Section 3(c)(3) (b)(I), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____	
<input type="checkbox"/> Check if this is a new address		

Section - II

<input type="checkbox"/> Amendment - Explain below.	<input type="checkbox"/> Final printed labels in response to Agency letter dated _____
<input type="checkbox"/> Resubmission in response to Agency letter dated _____	<input type="checkbox"/> "Me Too" Application
<input checked="" type="checkbox"/> Notification - Explain below.	<input type="checkbox"/> Other - Explain below

Explanation: Use additional page(s) if necessary. (For Section I and Section II.)**NOTIFICATION**

NON PRIA ACTION. Please see attached for more detail.

SEP 27 2010

Enclosed for Agency acceptance is a draft label for Advantage II Kitten (EPA Reg. No. 11556-150). The proposed revisions are the addition of the EPA Reg. No. and added the optional text: [Sample-not for (re)sale] for package sizes (SKUs).

Section - III

1. Material This Product Will Be Packaged In:				2. Type of Container	
Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No	Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No	Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Metal	<input type="checkbox"/> Plastic
	If "Yes" Unit Packaging wgt. No. per container	If "Yes" Package wgt. No. per container		<input type="checkbox"/> Glass	<input type="checkbox"/> Paper
*Certification must be submitted				<input type="checkbox"/> Other (Specify)	
3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container		4. Size(s) Retail Container		5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On labeling accompanying product	
6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled <input type="checkbox"/> Other _____					

Section - IV

1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application)		
Name Mary M. Hunt	Title Pesticide Registrations Manager	Telephone No. (Include Area Code) 913-268-2311
I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.		6. Date Application Received (Stamped)
2. Signature <i>Mary M. Hunt</i>	3. Title Pesticide Registrations Manager	
4. Typed Name Mary M. Hunt	5. Date 9-15-2010	

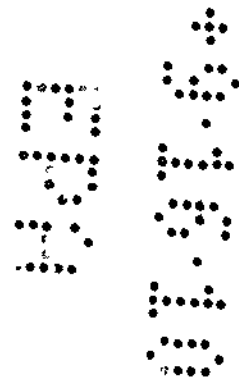
Bayer Health Care, Animal Health Division
Advantage II Kitten
EPA Reg. No. 11556-150
September 15, 2010

Section II Explanation

Enclosed for Agency acceptance is a draft label for Advantage II Kitten, EPA Reg. No. 11556-150.

The proposed revisions are the addition of the EPA registration number and the optional text, [Sample-not for (re)sale] to all package sizes (SKUs).

This notification is consistent with the provisions of PR Notice 98-10 and EPA regulations at 40 CFR 152.46 and no other changes have been made to the labeling or the confidential statement of formula of this product. Bayer understands that it is a violation of 18 U.S.C. Sec. 1001 to willfully make any false statement to EPA. Bayer further understands that if this notification is not consistent with the terms of PR Notice 98-10 and 40 CFR 152.46, this product may be in violation of FIFRA and Bayer may be subject to enforcement action and penalties under sections 12 and 14 of FIFRA.



Bayer HealthCare
Animal Health



September 15, 2010

Document Processing Desk (NOTIF)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle, Team 1

SUBJECT: *Notification of Label Revision to
Advantage II Kitten, EPA Reg. No. 11556-150
Advantage II Small Cat, EPA Reg. No. 11556-151
Advantage II Large Cat, EPA Reg. No. 11556-152*

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Ms. Eagle:

Please find enclosed for the Agency's review and acceptance, a Notification (EPA Form 8570-1 and attachment) and draft label dated September 15, 2010 for each subject product.

The proposed revisions are the addition of the EPA Registration Number and the addition of optional text, [Sample-not for (re)sale], to all package sizes (SKUs).

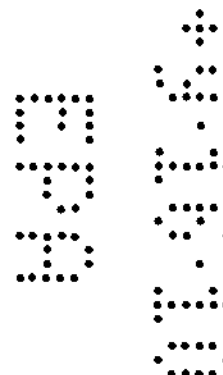
Thank you for your assistance with this notification process, and please contact me at 913-268-2311 or mary.hunt.b@bayer.com if you have any questions or need further information.

Respectfully,

BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION

Mary McKinney Hunt
Pesticides Regulatory Manager

Encl: (3) 8570-1 Application for Pesticide Notification
(3) Attachment to Application for Pesticide Notification
(3) Draft Label (3 cc each)
(3) Highlighted Label (1 cc each)



Reason To Issue: Added EPA Reg. No. and optional text
[Sample-not for (re)sale] for all SKUs

Date: 09/15/10
Supersedes: 06/17/10

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

Advantage® II Kitten

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older
For Use ONLY on Cats Weighing Under 5 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

[Selected optional claims bulleted here from page 6 and/or 7]

-
-
-
-
-
-
-
-
-
-

NOTIFICATION
SEP 27 2010

<u>Active Ingredients</u>	<u>% By Weight</u>
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

EPA Reg No. 11556-150

EPA Est. No. 11556-DEU-1

KEEP OUT OF REACH OF CHILDREN

CAUTION

[See back panel for First Aid.]

[For Directions For Use, and Storage and Disposal (instructions),
see supplemental labeling inside.]

Reason To Issue: Added EPA Reg. No. and optional text
[Sample-not for (re)sale] for all SKUs

Date: 09/15/10
Supersedes: 06/17/10

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on kittens under 8 weeks of age. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats. If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product.

If your cat is experiencing an adverse event, contact your veterinarian and, call 1-800-422-9874.

FIRST AID	
If Swallowed:	<ul style="list-style-type: none">• Call a poison control center or doctor immediately for treatment advice.• Have person sip a glass of water if able to swallow.• Do not induce vomiting unless told to do so by the poison control center or doctor.• Do not give anything to an unconscious person.
If In Eyes:	<ul style="list-style-type: none">• Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.• Call a poison control center or doctor for treatment advice.
If On Skin	<ul style="list-style-type: none">• Wash with plenty of soap and water.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For medical emergencies call 1-800-422-9874. For customer questions call 1-800-255-6826.	
NOTE TO PHYSICIAN	
Treat the patient symptomatically.	

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.



HOW TO APPLY

1. Use only on cats and kittens. Do not use on other animals.
2. Remove one applicator tube from the package. See "HOW TO OPEN" section.
3. Hold applicator tube in an upright position. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

[Visuals Depicting Application to Animal]

6. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. ***Do not get this product in your cat's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment.*** Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.
7. Discard empty tube as described in Storage and Disposal.
8. Under normal conditions the product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not retreat more often than once every 14 days. After flea control is attained, return to a monthly retreatment schedule.

ADDITIONAL INFORMATION

The successive feeding activity of fleas on cats may elicit a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage® II Kitten kills fleas and may reduce the incidence of this condition.

Advantage® II Kitten kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage® II Kitten treated cat. Advantage® II Kitten provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations.

Advantage® II Kitten kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Kitten is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place.

Pesticide Disposal and Container Handling: Nonrefillable container. **If Empty:** Do not reuse this container. Place in trash or offer for recycling if available. **If partly filled:** Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

Reason To Issue: Added EPA Reg. No. and optional text
[Sample-not for (re)sale] for all SKUs

Date: 09/15/10
Supersedes: 06/17/10

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Net Contents: XX Tube(s) - each 0.0078 fl. oz. (0.23 mL)

[Sample – Not for (Re)Sale]

Manufactured For

Bayer HealthCare LLC
Animal Health Division

P.O. Box 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

OPTIONAL MARKETING CLAIMS

- For use on cats and kittens 8 weeks of age and older
- Advantage II contains [imidacloprid], [and an/the] [insect growth regulator] [IGR] [pyriproxyfen]
- A single topical application remains effective for up to [4 weeks] [a month]
- Convenient, easy to apply topical solution
- Convenient, easy to apply and fragrance free [monthly] [topical solution]
- Once a month topical flea prevention and treatment for cats 8 weeks of age or older
- Advantage II is indicated for the prevention and treatment of fleas on cats 8 weeks of age and older
- For the prevention and treatment of flea infestations
- One treatment prevents further flea infestations for up to [4 weeks] [a month]
- Kills fleas on cats within [12] hours and continues to prevent infestations for up to [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the cat's environment are killed following contact with an Advantage II treated cat
- Kills larval stages of fleas following contact with an Advantage II treated cat
- Kills fleas within [12] hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Reinfesting fleas are killed within 2 hours with protection against further flea infestation
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- [Kills] [Controls] all flea life stages
- Comprehensive flea prevention and treatment
- 3-way flea protection ([kills][controls]) adults, larvae, and eggs
- [Prevents] [Stops] flea eggs from developing into [(biting) (adult)] fleas
- Treatment with Advantage II kills fleas and may reduce the incidence of flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and ovide
- Kills flea eggs
- Controls flea problems
- Provides flea protection
- Controls existing fleas and flea eggs plus [and] [prevents] future flea infestations
- Advantage II may be used year-round for flea [prevention][protection]

Reason To Issue: Added EPA Reg. No. and optional text
[Sample-not for (re)sale] for all SKUs

Date: 09/15/10
Supersedes: 06/17/10

- Contains an insect growth regulator (IGR) to kill flea eggs and prevent re-infestation
- Monthly use of Advantage II kills fleas and may prevent ([flea allergy dermatitis][flea bite hypersensitivity])
- Controls existing flea infestations on your cat and prevents further infestations
- Remains effective after bathing
- Remains effective following shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance free
- In child-resistant packaging
- Starts working through contact

Reason To Issue: Added EPA Reg. No. and optional text
[Sample-not for (re)sale] for all SKUs

Date: 09/15/10
Supersedes: 06/17/10

(Label on Individual Tube)

Advantage® II Kitten

9.10% Imidacloprid

0.46% Pyriproxyfen

0.0078 fl. oz. (0.23 mL)

EPA Reg. No. 11556-150

Keep Out of Reach of Children

CAUTION

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Material to be added to an e-Jacket/Jacket

Reg. No. 11556-150

Decision # 424201

Description:

new registration

1. Placement within the e-Jacket/jacket:

- ☐ Default: (chronological, top = newest)
- ☐ File Location: (eg. "before page 45 in .pdf")

2. ☒ Send to Data Extraction contractors this material:

- ☒ Newly stamped accepted label
- ☐ Notification
- ☐ New CSF
- ☐ Other: _____

3. Attach this coversheet to the top of the material or jacket. It must be well organized and clipped together, NOT STAPLED. Then give the material with this coversheet to staff in the Information Services Center (Room S-4900).

Reviewer: XLB

Division: RD

Phone: 306-0415

Date: 6-24-10

Material to be added to an e-Jacket/Jacket

Reg. No. 11556-150

Decision # 437863

Description:

new CSF

1. Placement within the e-Jacket/jacket:

- ☐ Default: (chronological, top = newest)
- ☐ File Location: (eg. "before page 45 in .pdf")

2. ☒ Send to Data Extraction contractors this material:

- ☐ Newly stamped accepted label
- ☐ Notification
- ☒ New CSF
- ☐ Other: _____

3. Attach this coversheet to the top of the material or jacket. It must be well organized and clipped together, NOT STAPLED. Then give the material with this coversheet to staff in the Information Services Center (Room S-4900).

Reviewer: 

Division: RD

Phone: 306-0415

Date: 8-6-10



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Dr. Doug Spilker
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201

JUL 30 2010

Dear Dr. Spilker:

Subject: Revised Basic Confidential Statements of Formula
Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)
Submission Date: July 22, 2010

The Agency has reviewed your submission for revised Confidential Statements of Formula, and the following comment applies:

The Confidential Statements of Formula dated July 20, 2010 for the basic formulations agree with the label claim in compliance with PR Notice 91-2 and are acceptable.

The Confidential Statements of Formula have been added to your file as part of the record and will replace the previously accepted basic Confidential Statements of Formula dated November 20, 2009. If you have any questions concerning this letter, please contact Kable Bo Davis at (703) 308-0415 or davis.kable@epa.gov.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Kable Bo Davis", with a stylized flourish at the end.

Venus Eagle
Product Manager (01)
Insecticide-Rodenticide Branch
Registration Division (7505P)

Bayer HealthCare
Animal Health



Via Federal Express

July 22, 2010

Office of Pesticide Programs (7504P) – Amendments/NonPRIA
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM 01

Subject: Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)

Dear Ms. Eagle:

Enclosed please find applications for the revision of the Confidential Statements of Formula for the subject products. **All of the revisions are identical for all three products, so we would appreciate it if all three actions be assigned to the same reviewer.** Furthermore, the formula revisions are identical to those recently accepted by the Agency for:

Advantage II Small Dog (EPA Reg. No. 11556-128)
Advantage II Medium Dog (EPA Reg. No. 11556-125)
Advantage II Large Dog (EPA Reg. No. 11556-127)
Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Although these are amendments, there are no data to review, and we hope that these could be expedited during the review and acceptance process.

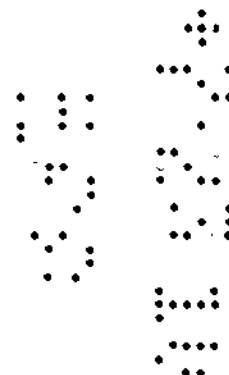
If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely,

Douglas A. Spilker, Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker.b@Bayer.com

Enclosures: 3 Applications for Amendment, dated 07/22/10

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390



Via Federal Express

July 22, 2010

Document Processing Desk
(Amend – Non-PRIA Action)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle, PM Team 01
Registration Division

Advantage II Kitten (EPA Reg. 11556-150)

- a. Form 8570-1 Application for Amendment
- b. Attachment to Application (1 page)
- c. Confidential Statement of Formula, dated 07/20/10 (2 copies)
- d. Confidential Statement of Formula, dated 11/20/09 (Supersedes) –
Original Product Name *Advantage IGR 5*

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ATTACHMENT FOR OPP
APPLICATION FOR PESTICIDE AMENDMENT
Page 1 of 1

Advantage II Kitten, EPA Reg. No. 11556-150
July 20, 2010

Enclosed for Agency acceptance are two (2) copies of the draft **Confidential Statement of Formula**, dated July 20, 2010 for Advantage II Kitten, EPA Reg. No. 11556-150, which supersedes the current Basic CSF on file with the Agency, dated November 20, 2009 (attached).

The proposed changes only include those described below:

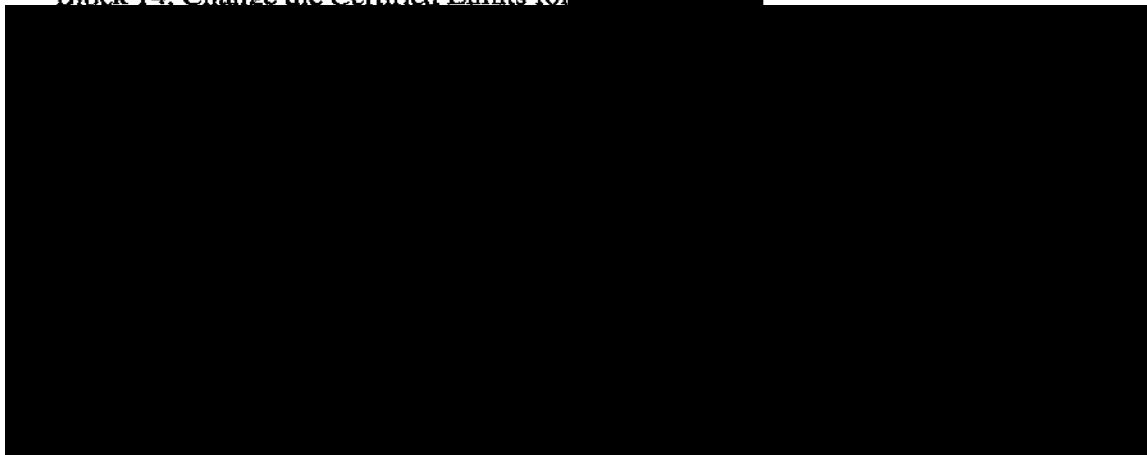
Block 3. Update Product Name

from: Advantage IGR 5
to: Advantage II Kitten

Block 4. Complete Registration No.

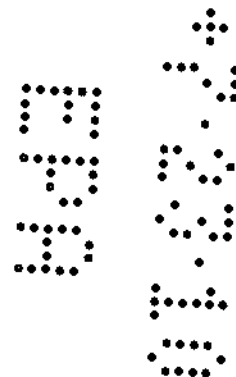
from: 11556-XXX
to: 11556-150

Block 14. Change the Certified Limits for



Block 21. Update the Date

from: 11/20/2009
to: 7/20/2010



Print Form

Please read instructions on reverse before completing form.

Form Approved OMB No. 2070-0080. Approval expires 2-28-



United States
Environmental Protection Agency
Washington, DC 20480

☐ Registration
☒ Amendment
☐ Other

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number 11556-150	2. EPA Product Manager V. Eagle	3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted
4. Company/Product (Name) Advantage II Kitten	PM# Team 01	
5. Name and Address of Applicant (Include ZIP Code) Bayer HealthCare LLC, Animal Health Division P. O. Box 390 Shawnee Mission, KS 66201-0390 <input type="checkbox"/> Check if this is a new address	6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____	

Section - II

<input checked="" type="checkbox"/> Amendment - Explain below.	<input type="checkbox"/> Final printed label in response to Agency letter dated _____
<input type="checkbox"/> Resubmission in response to Agency letter dated _____	<input type="checkbox"/> "Me Too" Application.
<input type="checkbox"/> Notification - Explain below.	<input type="checkbox"/> Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Enclosed for Agency acceptance are 2 copies of the Confidential Statement of Formula, dated 07/20/10, revised to widen the certified limits for [redacted] and update other information. Please see attached for further information. Minor formulation change (no data to review); Non-PRIA action.

Section - III

1. Material This Product Will Be Packaged In:				2. Type of Container	
Child-Resistant Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No	Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No	Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> Text <input type="checkbox"/> No		<input type="checkbox"/> Metal	<input type="checkbox"/> Plastic
* Certification must be submitted				<input type="checkbox"/> Glass	<input type="checkbox"/> Paper
If "Yes" Unit Packaging wgt. No. per container		If "Yes" Package wgt. No. per container		Other (Specify) _____	
3. Location of Not Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container		4. Size(s) Retail Container		5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product	
6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled				<input type="checkbox"/> Other _____	

Section - IV

1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)			
Name Douglas A. Spilker, Ph. D. (doug.spilker.b@bayer.com)		Title Manager, EPA Regulatory Affairs	
		Telephone No. (Include Area Code) 913-268-2751	
<p align="center">Certification</p> <p>I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.</p>			
2. Signature 		3. Title Manager, EPA Regulatory Affairs	
4. Typed Name Douglas A. Spilker, Ph. D.		5. Date 07/22/2010	
<p align="right">Date Application Received (Stamped)</p>			

Fee for Service

{879034,~

This package includes the following

- ☐ New Registration
- ☒ Amendment

- ☐ Studies? ☐ Fee Waiver?
- ☐ volpay % Reduction: _____

for Division

- ☐ AD
- ☐ BPPD
- ☒ RD

Risk Mgr. 1

Receipt No.

S-

879034

EPA File Symbol/Reg. No.

11556-150

Pin-Punch Date:

7/23/2010

☒ This item is NOT subject to FFS action.

Action Code:

Requested:

Granted:

Amount Due: \$ _____

Inerts approved: S. Lock 7/29/10

Parent/Child Decisions:

☒ Inert Cleared for Intended Use

☐ Uncleared Inert in Product

Reviewer: 10MP/kins

Date: 7-26-10

Remarks:



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

July 26, 2010

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DOUGLAS A. SPILKER, PH.D.
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

PRODUCT NAME: ADVANTAGE II KITTEN
COMPANY NAME: BAYER HEALTHCARE LLC
OPP IDENTIFICATION NUMBER:
EPA FILE SYMBOL: 11556-150
EPA RECEIPT DATE: 07/23/10

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application appears to qualify for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability for fast track status.

If you have any questions, please contact Registration Division, Risk Management Team 1, at (703) 308-8045.

Sincerely,

A handwritten signature in cursive script, appearing to read "P. A. Novak".

Front End Processing Staff
Information Services Branch
Information Technology & Resources Management Division

FAST-TRACK AMENDMENTS-Completeness Screening Checklist

Experts In-Processing Signature: S. H. H.EPA Reg. Number: 11556-100EPA Receipt Date: 7/23/10

	Checklist Item	Yes	No	NA
1	Application Form (EPA Form 8570-1) - signed?	Y		
2	Confidential Statement of Formula (EPA Form 8570-29) - signed?	Y		
3	Certification with Respect to Citation of Data (EPA Form 8570-34) signed?			Y
4	Formulator's Exemption Statement (EPA Form 8570-27) - signed?			Y
5	Data Matrix (EPA Form 8570-35) [Applicable, for adding me-too uses]			Y
	a) Selective Method?			
	b) Cite-All Method? Applicant owns data or list only the companies offered to pay			
	c) Public copy of Matrix provided? See PR Notice 98-5			
6	Is Label Included? (5 copies)			Y
	Comments:			
	<i>Matrix approved</i>			



U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Ave., N.W.
Washington, D.C. 20460

EPA Reg. Number:

11556-150

Date of Issuance:

JUN 24 2010

NOTICE OF PESTICIDE:

☒ Registration
☐ Reregistration

(under FIFRA, as amended)

Term of Issuance:

FROM: June 24, 2010
TO: see comment #1

Name of Pesticide Product:

Advantage II Kitten

Name and Address of Registrant (include ZIP Code):

Attention: Dr. Doug Spilker
Bayer HealthCare, LLC
P.O. Box 390
Shawnee Mission, KS 66201

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is conditionally registered in accordance with FIFRA section 3(c)(7)(A) provided that:

1. This registration is time-limited and expires two years from the date this product is first released for shipment. You must provide the Agency with a projected release for shipment date in writing within 30 days of the date of this Notice of Registration. The Agency will calculate the expiration date based on the projected release for shipment date until an actual release for shipment date is provided in writing.
2. Only one basic confidential statement of formula will be on file for this product at any one time; no alternate formulations or minor formulation amendments will be submitted or approved for this product.

Signature of Approving Official:

Venus Eagle; Product Manager (01)
Insecticide-Rodenticide Branch, Registration Division (7505P)

Date:

JUN 24 2010

3. You must submit quarterly enhanced incident reports and quarterly sales information in doses sold for this product beginning July 1, 2010.

Please flag any Confidential Business Information as such. Enhanced incident reporting should be submitted to the Product Manager. Quarterly sales information should be submitted to the Registration Division, Immediate Office (attn: Kimberly Nesci).

The following is a list of information that must be included in the quarterly reports for each incident:

- a. EPA Registration Number
 - b. Product Name (brand name)
 - c. Lot Number
 - d. Where Purchased: Internet, Store, Veterinarian
 - e. Active Ingredient(s)
 - f. Weight Range for Product
 - g. Date on which incident occurred (mm/dd/yyyy).
 - h. State in which the incident occurred (standard 2 letter abbreviation).
 - i. Registrant Case Number
 - j. Species: Dog, Cat, Other (specify)
 - k. Breed: (as reported by pet owner)
 - l. Age: Months or Years
 - m. Sex: Male, Female
 - n. Weight: Pounds
 - o. Primary Route of Exposure: Dermal, Oral, Other Animal, Inhalation, Other
 - p. Body System: Neurological, Dermatological, GI, Respiratory, Ocular, Other
 - q. Major Signs: Separate Column for Each Sign, Using Standard Terminology
 - r. Time to Onset: Hours, Days
 - s. Treated By Veterinarian: Yes or No
 - t. First Time Product Used: Yes or No
 - u. Misuse: Use on Incorrect Species, Overdose, Too Frequent Dosing, Other (describe)
 - v. Any Known Precondition
 - w. EPA Severity Code: Death, Major, Moderate, Minor
 - x. Outcome: Died, Recovered, Still Being Treated, Unknown
4. You must submit and/or cite all data required for registration of your product under FIFRA Section 3(c)(5) when the Agency requires all registrants of similar products to submit such data, and submit acceptable responses required for reregistration of your product under FIFRA Section 4.
 5. Revise the EPA Registration Number to read "EPA Registration No. 11556-150" on the first page of the label.
 6. Along with the enhanced incident reporting, you must submit an analysis of the incidents seen, to include the following details:

- a. All incidents should be reported including all minor dermal and ocular irritation reports.
 - b. Summary table for cats showing number of incidents of each severity code for each route of exposure. Each incident should only be reported once. If one incident has several routes of exposure, the order should be as follows: 1) ocular, 2) oral and 3) dermal. In other words, an incident with both oral and dermal exposure would be reported as oral exposure, and an incident with both ocular and oral exposure would be reported as ocular exposure.
 - c. A similar summary table for dogs (misuse or secondary exposure) showing number of incidents of each severity code for each route of exposure.
 - d. Summary table for dogs and table for cats showing number of incidents that are believed due to secondary exposure (e.g., multi-pet households).
 - e. A summary table for cats showing number of incidents for each severity code for following age ranges: 1) <3 months, 2) 3 – 6 months, 3) 6 – 9 months, 4) 9 – 12 months, 5) 1 year, 6) 2 years, 7) 3 years, 8) 4 years, 9) 5 years, 10) 6 years, 11) 7 years, 12) 8 years, 13) 9 years, 14) 10 years, 15) 11 years, 16) 12 years, 17) 13 years, 18) 14 years, 19) 15 years and 20) >15 years.
 - f. A summary table showing the number of cats incidents for each severity code for each pet weight range on the product label, if applicable.
 - g. A summary table for cat weight showing number of incidents for each product weight range. This table should show number of incidents in cats weighing less than that product weight range, number of incidents in cats in lower half of weight range, number of incidents in cats in upper half of weight range, and cats weighing more than the product weight range, if applicable.
 - h. Table showing number of incidents for each cat breed, where provided.
 - i. Table showing number of incidents in cats for each clinical sign.
 - j. Table showing number of incidents in cats for each organ system.
 - k. Report aggregate incidents, but do not combine moderate and minor incidents.
7. The Agency reserves the right, in the future, to require the addition of a section of label that lists the most common side effects, based on the submission of incident data.
 8. The required storage stability (830-6317) and corrosion characteristics (830-6320) data were submitted to the Agency on May 12, 2010 and are currently under review (D378289). If the data are deemed unacceptable, additional storage stability and corrosion characteristics data must be submitted and deemed acceptable.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions. A stamped copy of the label is enclosed for your records. If you have any questions regarding this notice, please contact Kable Bo Davis at (703) 306-0415 or davis.kable@epa.gov.

Venus Eagle, PM (01)
Insecticide-Rodenticide Branch
Registration Division (7505P)

Enclosure- Stamped Label

Reason To Issue: Propose registration

Date: 06/17/10
Supersedes: 11/24/09

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

Advantage® II Kitten

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older
For Use ONLY on Cats Weighing Under 5 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

[Selected optional claims bulleted here from page 6 and/or 7]

•
•
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•
•
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•
•

**ACCEPTED
with COMMENTS
In EPA Letter Dated:
JUN 24 2010**

*Under the Federal Insecticide,
Fungicide, and Rodenticide Act,
as amended, for the pesticide
registered under EPA Reg. No.
11556-150*

<u>Active Ingredients</u>	<u>% By Weight</u>
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

EPA Reg No. 11556-RLN

EPA Est. No. 11556-DEU-1

KEEP OUT OF REACH OF CHILDREN

CAUTION

[See back panel for First Aid.]

[For Directions For Use, and Storage and Disposal (instructions),
see supplemental labeling inside.]

Reason To Issue: Propose registration

Date: 06/17/10

Supersedes: 11/24/09

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on kittens under 8 weeks of age. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats. If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product.

If your cat is experiencing an adverse event, contact your veterinarian and, call 1-800-422-9874.

FIRST AID	
If Swallowed:	<ul style="list-style-type: none">• Call a poison control center or doctor immediately for treatment advice.• Have person sip a glass of water if able to swallow.• Do not induce vomiting unless told to do so by the poison control center or doctor.• Do not give anything to an unconscious person.
If In Eyes:	<ul style="list-style-type: none">• Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.• Call a poison control center or doctor for treatment advice.
If On Skin	<ul style="list-style-type: none">• Wash with plenty of soap and water.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For medical emergencies call 1-800-422-9874. For customer questions call 1-800-255-6826.	
NOTE TO PHYSICIAN	
Treat the patient symptomatically.	

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.



HOW TO APPLY

1. Use only on cats and kittens. Do not use on other animals.
2. Remove one applicator tube from the package. See "HOW TO OPEN" section.
3. Hold applicator tube in an upright position. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

[Visuals Depicting Application to Animal]

6. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. ***Do not get this product in your cat's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment.*** Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.
7. Discard empty tube as described in Storage and Disposal.
8. Under normal conditions the product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not retreat more often than once every 14 days. After flea control is attained, return to a monthly retreatment schedule.

ADDITIONAL INFORMATION

The successive feeding activity of fleas on cats may elicit a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage® II kills fleas and may reduce the incidence of this condition.

Advantage® II kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage® II treated cat. Advantage® II provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations.

Advantage® II kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place.

Pesticide Disposal and Container Handling: Nonrefillable container. **If Empty:** Do not reuse this container. Place in trash or offer for recycling if available. **If partly filled:** Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

Reason To Issue: Propose registration

Date: 06/17/10
Supersedes: 11/24/09

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Net Contents: [(One)(Four)] Tube(s) - 0.0078 fl. oz. (0.23 mL) each

OPTIONAL CLAIM FOR THE ONE TUBE PACKAGE: [Sample – Not for (Re)Sale]

Manufactured For
Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

OPTIONAL MARKETING CLAIMS

- For use on cats and kittens 8 weeks of age and older
- Advantage II contains [imidacloprid], [and an/the] [insect growth regulator] [IGR] [pyriproxyfen]
- A single topical application remains effective for up to [4 weeks] [a month]
- Convenient, easy to apply topical solution
- Convenient, easy to apply and fragrance free [monthly] [topical solution]
- Once a month topical flea prevention and treatment for cats 8 weeks of age or older
- Advantage II is indicated for the prevention and treatment of fleas on cats 8 weeks of age and older
- For the prevention and treatment of flea infestations
- One treatment prevents further flea infestations for up to [4 weeks] [a month]
- Kills fleas on cats within [12] hours and continues to prevent infestations for up to [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the cat's environment are killed following contact with an Advantage II treated cat
- Kills larval stages of fleas following contact with an Advantage II treated cat
- Kills fleas within [12] hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Reinfesting fleas are killed within 2 hours with protection against further flea infestation
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- [Kills] [Controls] all flea life stages
- Comprehensive flea prevention and treatment
- 3-way flea protection ([kills][controls]) adults, larvae, and eggs
- [Prevents] [Stops] flea eggs from developing into [(biting) (adult)] fleas
- Treatment with Advantage II kills fleas and may reduce the incidence of flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and oocide
- Kills flea eggs
- Controls flea problems
- Provides flea protection
- Controls existing fleas and flea eggs plus [and] [prevents] future flea infestations
- Advantage II may be used year-round for flea [prevention][protection]

Reason To Issue: Propose registration

Date: 06/17/10

Supersedes: 11/24/09

- Contains an insect growth regulator (IGR) to kill flea eggs and prevent re-infestation
- Monthly use of Advantage II kills fleas and may prevent ([flea allergy dermatitis][flea bite hypersensitivity])
- Controls existing flea infestations on your cat and prevents further infestations
- Remains effective after bathing
- Remains effective following shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance free
- In child-resistant packaging
- Starts working through contact

Reason To Issue: Propose registration

Date: 06/17/10
Supersedes: 11/24/09

(Label on Individual Tube)

Advantage® II Kitten

9.10% Imidacloprid

0.46% Pyriproxyfen

0.0078 fl. oz. (0.23 mL)

EPA Reg. No. 11556-RLN

Keep Out of Reach of Children

CAUTION

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Proposed Cat Spot-On Products (EPA File Symbol 11556-RLN, 11556-RLE and 11556-RLR) - rev labels

Doug Spilker

to:

Kable Davis

06/17/2010 04:00 PM

Show Details

resubmission

History: This message has been replied to.

Hi Bo,

Please find attached the labels revised according to your email of 6/16/10. Regarding Item 4, it is our position that these labels for a new product already contain proactive warning in the "HOW TO APPLY" section - Item 6, based on our experience with other imidacloprid-containing spot-on products. I have attached both a highlighted and clean version of each. As we discussed previously, I have made a couple of other changes including: a) change in primary brand names, b) addition of single tube information and "Not for Sale" optional language, and c) an additional claim for "Starts working through contact" - which is on our other Advantage II products.

I look forward to our discussion and finalizing of these registrations.

We accept your invitation to discuss with you and Ms. Nesci the "potential side effect" issue in a conference call next Tuesday, June 22, at 10:00 am (EDT). If you would like, I can set up a teleconference number for our use. please let me know.

best regards,

Doug

Doug Spilker
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Country: USA

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Proposed Cat Spot-On Products (EPA File Symbol 11556-RLN, 11556-RLE and 11556-RLR)

Kable Davis to: Doug Spliker

06/16/2010 11:41 AM

Cc: Venus Eagle

Doug-

I have finished my review of the proposed labels for EPA File Symbols 11556-RLN, 11556-RLE and 11556-RLR. However, I want to first acknowledge that we have already discussed renaming these products and you will incorporate these new names into the revised labels. The following changes are required:

Label Changes (pages 1 - 5)

Note: Because the name of the product is different for each submission (EPA File Symbols 11556-RLN, 11556-RLE and 11556-RLR), my comments will simply say "(Name of Product)". This allows the comment to be applicable to all three products.

1. The efficacy data that supports biting lice on dogs cannot be used to support claims for the control of biting lice on cats. All references to lice must be deleted from the label.
2. Each of the three proposed cat products contain one of the following statements: "...weighing 5 lbs and under", ".....weighing 5 to 9 lbs" and ".....weighing 9 lbs and over". The labels must be revised to clearly explain which product is appropriate for cats weighing 5 pounds and 9 pounds.
3. The first page of each label contains a claim similar to "*Once-A-Month Topical Flea and Lice Prevention and Treatment for Cats and Kittens 8 Weeks and Older and Weighing 5 lbs and Under*". Revise these statements to be read as follows (the sizes will change depending upon the product).

"*Once-A-Month Topical Flea Prevention and Treatment for Cats.*"
"*For use ONLY on Cats 8 Weeks and Older.*"
"*For use ONLY on Cats Weighing.....*"
4. The label needs to include a list of potential side effects (based on most common incidents seen). The Agency is allowing each registrant to come up with these statements themselves and then submit for approval. If you are unable to provide these statements prior to registration, the Agency will include this requirement in the registration notice as a condition of registration.
5. On page 2 of the label, revise "*animals*" to read "*cats*", "*pets*" to read "*cats*" and "*animal*" to read "*cat*".
6. Revise the FIRST AID section into a boxed format per PR-Notice 2001-1. The following link provides an example. http://www.epa.gov/PR_Notices/pr2001-1.pdf
7. Currently, the proposed label contains a phone number of consumer questions and another for medical emergencies. The label must also include a third phone number for cats experiencing adverse reactions. Include the following statement "*If your cat is experiencing an adverse event, contact your veterinarian and call.....*"
8. On page 4, revise "*GENERAL INFORMATION*" to read "*USE INFORMATION*".
9. On page 4, revise "*Treatment of cats with (Name of Product) rapidly kills fleas and reduces the incidence of this condition.*" to read "*Treatment of cats with (Name of Product) kills fleas and may reduce the incidence of this condition.*"
10. On page 4, revise "*Monthly treatments are required for optimal control and prevention of fleas.*" to

read "Apply monthly for optimal control and prevention of fleas."

11. Within the "USE INFORMATION" section of the label (page 4), revise "pet's" and "pet" to read "cat's" and "cat".

12. On page 4 of the label, revise "(Name of Product) provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations." to read "(Name of Product) provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations."

13. On page 4 of the label, revise "(Name of Product) kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage." to read "(Name of Product) kills adult fleas, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage."

14. On page 4, revise "(Name of Product) is waterproof and remains effective following a shampoo treatment, swimming or after exposure to rain or sunlight." to read "(Name of Product) is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight."

15. On page 4, revise "Storage." to read "Pesticide Storage."

16. On page 4, revise "Disposal." to read "Pesticide Disposal."

Changes to Marketing Claims (pages 6 - 7)

Both IB (Insecticide Branch) and IRB (Insecticide-Rodenticide Branch) are working together to tighten up marketing claims found on pet spot-on products. The following label changes are required. Note: Because the name of the product is different for each submission (EPA File Symbols 11556-RLN, 11556-RLE and 11556-RLR), my comments will simply say "(Name of Product)". This allows the comment to be applicable to all three products.

1. Revise "A single topical application remains effective for [4 weeks][a month]" to read "A single topical application remains effective for up to [4 weeks][a month]"

2. Revise "One treatment prevents further flea infestations for [4 weeks][a month]" to read "One treatment prevents further flea infestations for up to [4 weeks][a month]"

3. Revise "Kills fleas on cats within [12] hours and continues to prevent infestations for [four weeks][a month]" to read "Kills fleas on cats within [12] hours and continues to prevent infestations for up to [four weeks][a month]"

4. Delete the claim "Kills larval stages of fleas in the cat's environment" or revise to read "Kills larval stages of fleas following contact with an (Name of Product) treated cat."

5. Delete the claim "Effectively targets all [life] stages [of fleas]." The product controls all life stages, however it doesn't "target" certain stages (such as pupal stage). This claim implies that the product directly targets pupae.

6. As stated above (#1 under label changes), data have not been submitted to support the addition of lice claims for cats. All claims concerning biting lice must be deleted.

7. Delete the claims that state "Dual Protection" or "3-way Flea Protection". If you choose to retain these claims, the statement must explain what is meant by "dual protection" or "3-way Flea Protection". Currently, the claims include optional language. If the optional language isn't used, the claims can imply heightened efficacy. This comment concerns the following proposed claims:

- "Dual protection (against fleas and lice)"
- "3-way flea protection ([kills][controls] adults, larvae, and eggs"
- "[Dual-Action][2-way] formula"

8. Delete the claim "[Prevents] [Stops] flea eggs [and flea larvae] from developing into [(biting)(adult)] fleas". If you choose to retain this claim, it must be reworded so that it explains that only larvae that come into contact with a cat treated with product will not develop into adult fleas.

9. Revise the claim "Treatment with (Name of Product) rapidly kills fleas and may reduce the incidence of flea allergic dermatitis [FAD] or flea bite hypersensitivity" to read "Treatment with (Name of Product) kills fleas and may reduce the incidence of flea allergic dermatitis [FAD] or flea bite hypersensitivity".

10. Delete the claim "Controls highly [limiting] [annoying] [flea] [insect] bites".

11. Revise the claim "Controls existing fleas and flea eggs plus [and] [prevents] future flea infestations [in the home]" to read "Controls existing fleas and flea eggs plus [and] [prevents] future flea infestations".

12. Revise the claim "Use flea [prevention][protection] year-round" to read "(Name of Product) may be used year-round for flea [prevention][protection]"

13. Revise the claim "Monthly use of (Name of Product) kills fleas to prevent ([flea allergy dermatitis][flea bite hypersensitivity])" to read "Monthly use of (Name of Product) kills fleas and may prevent ([flea allergy dermatitis][flea bite hypersensitivity])".

14. Revise the claim "Controls existing flea infestations and prevents further infestations in your home" to read "Controls existing flea infestations on your cat and prevents further infestations."

15. Delete the claim "Prevents fleas on treated cats from infesting (reinfesting) your home". This product is for control/prevention of fleas on cats and must not be confused as a product intended to treat or prevent home flea infestations.

16. Revise the claim "Remains effective after bathing and/or swimming" to read "Remains effective after bathing".

17. Revise the claim "Remains effective following swimming and/or shampooing" to read "Remains effective following shampooing".

To avoid any confusion in the future, I would like to remind you that you are not allowed to put unapproved claims on your company's website. All claims must be reviewed and accepted by the Agency. In addition, claims must be supported by data that have been reviewed and accepted by the Agency. I strongly recommend that if you or anyone else with Bayer is in anyway confused by these statements, to please give me, Venus Eagle (Product Manager 1) or Meredith Laws (IRB Branch Chief) a call to discuss.

When you are finished revising the labels for all three products, please email me both clean and highlighted copies. I will reply with electronic copies of the registration notices and stamped labels. In addition, I will mail you paper copies of the CRP and companion animal (for kittens) reviews.

If you have any questions, please give me a call or shoot me an email.

Enjoy the remainder of your Wednesday.

Sincerely,
Bo

Kable Bo Davis, MS
Entomologist

U.S. Environmental Protection Agency
Insecticide-Rodenticide Branch
Registration Division (7505P)
1200 Pennsylvania Ave. NW
Washington, DC 20460

Tel: 703 306-0415
Fax: 703 305-6596
Email: davls.kable@epa.gov

Advantage II (nee Advantage Plus) - Storage Stability Report Submission

Doug Spilker

to:

~~Autumn Metzger, Kable Davis~~

05/12/2010 10:44 AM

Show Details

resubmission

History: This message has been replied to and forwarded.

For your information. I sent to both of you since these data support both the current products as well as the pending products (i.e. all same formulation)

Best regards,

Doug

Doug Spilker
Manager - EPA Reg. Affairs
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Advantage IGR 5 (11556-RLN) - Follow-up on feeding discussion

Doug Spilker

to:

Byron Backus

04/21/2010 11:40 AM

Cc:

Kable Davis, Jennifer Schofield

Show Details

resubmission

Dear Dr. Backus,

Reference is made to the telephone conversation on April 9, 2010 between the Agency (B. Backus) and Bayer Animal Health (D. A. Spilker and J. Schofield) regarding the incidence and timing of the offering of moist food during the kitten study - "Evaluation of the General Safety of M881 (Bayer Report 33714; MRID 47924801)." Please find attached a document that is in response to this request for additional information, prepared by our Dr. Schofield.

The addendum to the aforementioned report, which includes the individual feeding data we previously sent you electronically, will be coming through normal channels (data processing desk) for entering into the Agency's archives.

If you need anything further, please call.

best regards,

Doug

Doug Spilker
Manager - EPA Reg. Affairs
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Re: Individual daily food consumption data (Bayer Report 33714; MRID 47924801)

Doug Spilker

to:

Byron Backus

04/09/2010 05:20 PM

resubmission

Cc:

Deborah McCall, Jennifer Schofield, Venus Eagle, Kable Davis
Show Details

Dear Dr. Backus,

Reference is made to your message below, and our follow-up telephone discussion (D. Spilker & J. Schofield with B. Backus) this afternoon regarding the subject Advantage IGR/kitten study currently under review.

Attached as you requested, please find: 1) the Excel spreadsheet with food consumption data and 2) a PDF file of the spreadsheet. Both documents include a legend which explains the color format: pink indicates food consumption of less than or equal to 25 grams and yellow indicates moist food offered with dry food ration (the total "amount consumed" reflects dry and moist food rations for these cells). The only exception to this formatting is for animal 5M3:08KPK1 on day 15 (food consumption 20 grams and moist food offered - food consumption formatting took priority over that included for moist food condition). This information is for your immediate use, and we understand that it should be properly formatted and sent through normal channels as soon as possible.

We have been in contact with the study director at Sinclair Labs regarding the other topics we discussed with you.

We will keep you updated on findings.

Please let us know if I can be of further assistance.

Best regards,
Doug

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Bayer Animal Health "Protecting.Curing.Caring...Together"

Backus.Byron@epamail.epa.gov

04/09/2010 10:07 AM

To Doug Spilker <doug.spilker.b@bayer.com>

cc McCall.Deborah@epamail.epa.gov

Subject Individual daily food consumption data

In order to complete the review on 11556-RLN we need to evaluate the individual daily food consumption data (days -7 through 28) for the kittens in Bayer Animal Health Study 152.141 (the EPA MRID no. is 47924801). As reported (p. 182-184) food consumption is expressed as a weekly average for each individual animal. You can send a pdf file. If you have any questions, please give me a call at 703-305-5704. Thanks - Byron T. Backus

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Additional CRP Data on CDs - Advantage Plus for Dogs

Doug Spilker

to:

~~Rosalind Gross~~

02/01/2010 04:55 PM

resubmission

Cc:

Autumn Metzger, Kable Davis

Show Details

Dear Ms. Gross,

As you requested, the additional copies of the CRP data for the dog studies are on their way. The Fedex tracking number is [REDACTED] - Sent "Priority over night" Attached is a copy of the cover letter for your information.

best regards,

Doug

Douglas A. Spilker, Ph.D.

Manager - EPA Reg. Affairs

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Advantage IGR products for Cats (EPA File Symbols 11556-RLN, -RLR, -RLE) - Additional CRP Info

Doug Spilker

to:

~~Rosalind Gross~~

01/14/2010 04:10 PM

Cc:

Autumn Metzger, Kable Davis, Harish Chopade

Show Details

resubmission

Dear Ms. Gross,

Reference is made to our telephone discussion yesterday, January 13, 2010, regarding the Child Resistant Packaging (CRP) testing as it relates to the subject products on cats. In the aforementioned discussion, with our Dr. Chopade and me, you requested the submission of some additional clarifying information regarding the CRP testing with children and senior adults that we submitted on December 3, 2009 to revise the packaging and respective use directions for these products.

Please find attached a chart, as you requested, that cross references the study numbers, MRID numbers and EPA registration numbers, with additional information including:

- a) further detail, in addition to what is in the reports, as to what constituted a failure in both the child and adult tests, and
- b) further clarification as to the exact number of cards (blister packs) given in each of the trials.

We understand that the information presented in this form is adequate for your use, and will become a part of the official file for review. If you need anything further, please do not hesitate to call.

Best regards,

Doug

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

April 15, 2010

MEMORANDUM

Subject: Name of Pesticide Product: ADVANTAGE IGR 5
EPA Reg. No. /File Symbol: 11556-RLN
DP Barcode: DP 372322
Decision No.: 424201
Action Code: R310
PC Codes: 129099 (Imidacloprid: 9.1%)
129032 (Pyriproxyfen: 0.46%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
04-15-2010

M. Hashu

To: Kable Davis/Venus Eagle, RM 01
Insecticide-Rodenticide Branch
Registration Division (7505P)

Registrant: BAYER HEALTHCARE LLC

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>	<u>By wt.</u>
129099 Imidacloprid	9.10%
129032 Pyriproxyfen	0.46%
<u>Other Ingredient(s):</u>	<u>90.44%</u>
TOTAL	100.00%

ACTION REQUESTED: The Risk Manager requests:

"...Please review the attached companion animal data for a new spot-on for cats and kittens. The cover letter details the regulatory history of this product. In addition to the cover letter, I also included copies of the proposed label, proposed csf and previous companion animal and protocol reviews..."

BACKGROUND:

The material received includes a companion animal safety study (in MRID 47924801) titled: "Evaluation of the General Safety of Imidacloprid + Pyriproxyfen Spot-On in 8-Week-Old Kittens"), a CSF, a proposed label for this product (Advantage® IGR 5), and a cover letter from the registrant dated November 30, 2009. The proposed product would be packaged in single-use tubes which would provide an application of 0.23 mL.

COMMENTS AND RECOMMENDATIONS:

1. The registrant is citing a previously reviewed cat companion animal safety study in MRID 45097001 to support this product's use on adult cats. A comparison of the CSF (dated November 20, 2009) for 11556-RLN with the analysis of the test material used in the study in MRID 45097001 (available from Documentum as MRID 45007001.CA.tif) indicates they are toxicologically similar. The study involved a 5X dose level of 2.0 mL (1X = 0.4 mL) for cats weighing less than 9 lbs and a 5X dose level of 4.0 mL (1X = 0.8 mL) for cats weighing >9 lbs. The test material (containing 9.1% Imidacloprid and 0.9% Pyriproxyfen) was applied on study days 0, 7, 14 and 21. On Day -1 the mean weight of the Group A (test material) females was 6.00 (S.D. = 0.56) lb, with a range from 5.23 to 6.92 lbs; the mean weight of the Group A males was 9.34 (S.D. = 1.16) lb, with a range from 8.27 to 10.9 lbs. All of the females weighed less than 9 lbs, and each was treated with 2.0 mL (mean amount: 0.3333 mL/lb). Two males weighed more than 9 lb, and were treated with 4.0 mL; the remaining 4 weighed less than 9 lbs and were each treated with 2.0 mL. The mean dosage for males on a body weight basis was 0.278 mL/lb. The mean 1X treatment for females was $(0.3333 \text{ mL/lb})/5 = 0.06666 \text{ mL/lb}$ and for males was $(0.278 \text{ mL/lb})/5 = 0.0556 \text{ mL/lb}$. A dosage of 0.23 mL would be supported for adult female cats ≥ 3.45 lbs and for adult male cats ≥ 4.13 lbs, and labeling (for adult cats) should be revised accordingly.

2. The name "Advantage" is being used by Bayer for both dog and cat products. One of the recommendations made as a result of the recent Agency adverse incident data analysis for pet spot-ons is the requirement for different brand names for dog and cat products.

3. The study (on 8-week-old kittens) in MRID 47924801 was reviewed in TRB, and was then secondarily reviewed in HED. This study has been classified as acceptable and can be used to support the proposed use of Advantage® IGR 5 in 8-week-old and older kittens, with an application rate of 0.23 mL and retreatment no more frequently than at 14 days.

4. The study in MRID 47924801 was conducted on test material consistent with that in the basic formulation CSF (dated November 20, 2010) for this product. The material received by this reviewer did not include any alternate formulation CSFs.

5. The following is the executive summary from the DER for MRID 47924801:

In a companion animal safety study (MRID 47924801), 5 groups, each containing 6 males and 6 females, of domestic shorthair kittens (54-57 days old on Day 0; Day -1 body weights: males: 0.691-1.012 kg; females: 0.555-0.935 kg; source: Liberty Research, Inc., Waverly, NY), were topically treated (on Day 0) with (Group 1): mineral oil at a total dose of 1.15 mL; (Group 2): 3X

vehicle substance at a total dose of 0.63 mL; (Group 3): 5X vehicle substance at a total dose of 1.05 mL; (Group 4): 3X test substance at a total dose of 0.69 mL; and (Group 5): 5X dose test substance at a total dose of 1.15 mL. For each group, the total dose was split into three sub-applications which were administered at approximately 60-minute intervals. The application site was the skin on the dorsal midline from the base of the skull to the interscapular region. The dosing was repeated on Day 14.

The groups and test materials they received (with amounts applied) are shown in the table below:

Group	Test Material Applied	Volume of each application	Cumulative amount applied on Day 0; also on Day 14
1	Mineral oil	1 st app = 0.35 mL; 2 nd & 3 rd = 0.4 mL	1.15 mL
2	Vehicle of proposed formulation (no active ingredients) at 3X	3 applications @ 0.21 mL	0.63 mL
3	Vehicle of proposed formulation (no active ingredients) at 5X	3 applications @ 0.35 mL	1.05 mL
4	Proposed formulation (with active ingredients) at 3X	3 applications @ 0.23 mL	0.69 mL
5	Proposed formulation (with active ingredients) at 5x	1 st app = 0.35 mL; 2 nd & 3 rd = 0.4 mL	1.15 mL

The animals were observed twice daily (morning and afternoon) except on days of treatment and on the first day following each dosage. On treatment days (0 and 14) kittens were observed pre-treatment, and at 1, 2, 3 and 4 hours (± 15 minutes) following completion of the third and final sub-application. On days 1 and 15, kittens were observed at approximately 8:00 am, 11:00 am, and 3:00 pm (± 30 minutes). Body weights were determined on days -7, -3, -1, 1, 15 and 28. Physical examinations were conducted by a veterinarian on days -7, -3, 1, 15 and 28.

Blood for hematology and clinical chemistry was collected from all the kittens on study days -7, 1 (approximately 21 hours post-treatment), 15 (approximately 24 hours post-treatment), and at termination on day 28. To avoid overstressing the kittens, only 1 to 3 mL of blood was collected at each time, consequently, coagulation times were not determined.

All animals survived to the end of the study.

All kittens showed hair coat effects at 1-4 hours post-dose, mostly on days 0 and 14, but in some cases these effects were noted on subsequent days, primarily in Group 1 (all 12 kittens on day 15, and in 5 on day 16), with a few occurrences in Group 2 (two kittens on day 15 and one on day 16), Group 3 (two kittens on day 15 and one on day 16) and one in Group 5 (day 15 only). One Group 3 female had hair coat effects on day 21.

One Group 5 male (08KPK1) was lethargic on day 15 (the day following the second dosage). This was the only reported occurrence of lethargy in the study; also it was the only kitten in this group with coat effects on day 15; this animal had shown diarrhea on day 14 pre-dose and on day 15. The overall mean food consumption of this animal (49.4 g/day) from week 1 to 4 was lower than values of the other males (range: 52.9 to 69.0 g/day) in this group, and was particularly low (36.6 g/day) during week 2 (presumably from day 7 through 13, a period that did not include an application of the test material). According to the report summary this kitten demonstrated intermittent anorexia (days 11 and 15) resulting in mild weight loss and transient dehydration

and lethargy, with immediate improvements in food consumption and general condition noted following supplementation of the diet with moist food.

All kittens gained weight from Day -1 to Day 28. Mean body weight gains of Group 5 (5X test material) males and females were noticeably lower than those of the other groups in the period from Day -1 to Day 20 (which included applications on Days 0 and 14). Group 5 males had a weight gain that was 87% of that for Group 1 males, and Group 5 females had a value that was 92.6% that of Group 1 females. Group 4 (3X test material) males and females had values slightly greater than those of their Group 1 counterparts.

It is concluded that the margin of safety in kittens administered topical application of the product formulation is at least 3X. Possible effects observed at 5X included lethargy in one male kitten following the second set of applications, and decreased body weight gains in both males and females in the period from day -1 to day 20. As noted in the current 870.7200 Guidelines: "Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-threatening signs)."

This companion animal safety study in male and female domestic shorthair kittens is Acceptable/Guideline and does satisfy the guideline requirement for a companion animal safety study (OPPTS 870.7200) in 54-57 day (8 week) kittens.

EPA Primary Reviewer: Byron T. Backus, Ph.D.
Technical Review Branch, Registration Division (7505PY)

Signature: Byron T. Backus
Date: 04/15/2010

EPA Secondary Reviewer: Ayaad Assaad, D.V.M., Ph.D.
Toxicology and Epidemiology Branch, HED (7509PY)

Signature: A. Assaad
Date: 04/15/2010
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Companion animal safety study- kittens – OPPTS 870.7200

PC CODES: 129099- Imidacloprid, 129032- Pyriproxyfen,

DP BARCODE: 372322

TEST MATERIAL (PURITY): M880 Insecticide (Bayer Imidacloprid/Pyriproxyfen/Dog/Cat SpotOn), Formula No. BB-06-139; Lot No. BB-06-139-M880-06-05-60; described as a clear amber liquid with a specific gravity of 1.095 g/mL (see p. 18 of MRID 47924801) containing 9.1% Imidacloprid and 0.46% Pyriproxyfen.

TRADE NAME: Advantage® IGR 5

CITATION: Madsen, T. (2009) Evaluation of the General Safety of M880. Bayer Animal Health Study No.: 152.141; In-Life Testing Facility Study No. S07648; Bayer Animal Health Report No.: 33714. Sinclair Research Center, Inc., 562 State Road DD, Auxvasse, MO 65231, 9 October 2009. MRID 47924801. Unpublished. 193 p.

SPONSOR: Bayer HealthCare LLC / Animal Health Division

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 47924801), 5 groups, each containing 6 males and 6 females, of domestic shorthair kittens (54-57 days old on Day 0; Day -1 body weights: males: 0.691-1.012 kg; females: 0.555-0.935 kg; source: Liberty Research, Inc., Waverly, NY), were topically treated (on Day 0) with (Group 1): mineral oil at a total dose of 1.15 mL; (Group 2): 3X vehicle substance at a total dose of 0.63 mL; (Group 3): 5X vehicle substance at a total dose of 1.05 mL; (Group 4): 3X test substance at a total dose of 0.69 mL; and (Group 5): 5X dose test substance at a total dose of 1.15 mL. For each group, the total dose was split into three sub-applications which were administered at approximately 60-minute intervals. The application site was the skin on the dorsal midline from the base of the skull to the interscapular region. The dosing was repeated on Day 14.

The groups and test materials they received (with amounts applied) are shown in the table below:

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5	Proposed formulation (with active ingredients) at 5x	1 st app = 0.35 mL; 2 nd & 3 rd = 0.4 mL	1.15 mL

The animals were observed twice daily (morning and afternoon) except on days of treatment and on the first day following each dosage. On treatment days (0 and 14) kittens were observed pre-treatment, and at 1, 2, 3 and 4 hours (\pm 15 minutes) following completion of the third and final sub-application. On days 1 and 15, kittens were observed at approximately 8:00 am, 11:00 am, and 3:00 pm (\pm 30 minutes). Body weights were determined on days -7, -3, -1, 1, 15 and 28. Physical examinations were conducted by a veterinarian on days -7, -3, 1, 15 and 28.

Blood for hematology and clinical chemistry was collected from all the kittens on study days -7, 1 (approximately 21 hours post-treatment), 15 (approximately 24 hours post-treatment), and at termination on day 28. To avoid overstressing the kittens, only 1 to 3 mL of blood was collected at each time, consequently, coagulation times were not determined.

All animals survived to the end of the study.

All kittens showed hair coat effects at 1-4 hours post-dose, mostly on days 0 and 14, but in some cases these effects were noted on subsequent days, primarily in Group 1 (all 12 kittens on day 15, and in 5 on day 16), with a few occurrences in Group 2 (two kittens on day 15 and one on day 16), Group 3 (two kittens on day 15 and one on day 16) and one in Group 5 (day 15 only). One Group 3 female had hair coat effects on day 21.

One Group 5 male (08KPK1) was lethargic on day 15 (the day following the second dosage). This was the only reported occurrence of lethargy in the study; also it was the only kitten in this group with coat effects on day 15; this animal had shown diarrhea on day 14 pre-dose and on day 15. The overall mean food consumption of this animal (49.4 g/day) from week 1 to 4 was lower than values of the other males (range: 52.9 to 69.0 g/day) in this group, and was particularly low (36.6 g/day) during week 2 (presumably from day 7 through 13, a period that did not include an application of the test material). According to the report summary this kitten demonstrated intermittent anorexia (days 11 and 15) resulting in mild weight loss and transient dehydration and lethargy, with immediate improvements in food consumption and general condition noted following supplementation of the diet with moist food.

All kittens gained weight from Day -1 to Day 28. Mean body weight gains of Group 5 (5X test material) males and females were noticeably lower than those of the other groups in the period from Day -1 to Day 20 (which included applications on Days 0 and 14). Group 5 males had a

weight gain that was 87% of that for Group 1 males, and Group 5 females had a value that was 92.6% that of Group 1 females. Group 4 (3X test material) males and females had values slightly greater than those of their Group 1 counterparts.

It is concluded that the margin of safety in kittens administered topical application of the product formulation is at least 3X. Possible effects observed at 5X included lethargy in one male kitten following the second set of applications, and decreased body weight gains in both males and females in the period from day -1 to day 20. As noted in the current 870.7200 Guidelines: "Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-threatening signs)."

This companion animal safety study in male and female domestic shorthair kittens is Acceptable/Guideline and does satisfy the guideline requirement for a companion animal safety study (OPPTS 870.7200) in 54-57 day (8 week) kittens.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance and [No] Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test materials:

1a. Control/reference substance (Group 1)

Description:	Mineral oil, light, from Fisher Chemical, a clear colorless viscous liquid
Lot no.:	084662
Purity:	
Storage:	"Controlled room temperature"
Compound Stability:	
CAS #:	8042-47-5

1b. Vehicle Control; M880 Insecticide Placebo (Group 2 at 3X; Group 3 at 5X))

Description:	Clear amber liquid
Lot no.:	08-05-30
Purity:	LOD (<0.018%) Pyriproxyfen; LOD (<0.01%) Imidacloprid
Storage:	"Controlled room temperature"
Compound Stability:	
CAS #:	Not reported

1c. M880 Insecticide (Bayer Imidacloprid/Pyriproxyfen/Dog/Cat Spot On)

Description: Clear amber liquid
Lot no.: 011902-09
Purity: 0.46% w/w Pyriproxyfen; 9.1% Imidacloprid
Storage: At room temperature
Compound Stability: Expiration date: January 19, 2011
CAS #: 95737-68-1 (Pyriproxyfen); 138261-41-3 (Imidacloprid)

2. Vehicle control: See control substance described in 1d above

3. Test animals:

Species: Cat
Strain: Domestic shorthair
Age/weight: Day 0: 54-57 days old; males: 0.691-1.012 kg; females: 0.555-0.935 kg
Source: Liberty Research, Inc., Waverly, NY
Housing: Individually housed in 3 ft x 3 ft stainless steel pens
Diet: Purina® Kitten Chow or equivalent, 150 g/kitten/day; animals that exhibited inappetance (= consumption \leq 25 g/kitten/day) were offered 20 to 75 g of moist food (Purina® Friskies, Mariner's Catch) per day.
Water: Well water, sourced from an on-site deep well, *ad libitum*
Environmental conditions:
Temperature: 67-87° F
Humidity: \leq 15-86%
Air changes: "appropriate hourly air exchanges."
Photoperiod: 12 hours light/12 hours dark
Acclimation period: One week

B. STUDY DESIGN:

- 1. In life dates:** Start: February 2, 2009; End: March 9, 2009. Day 0 for Replicate A was February 2 and for Replicate B was February 9.
- 2. Animal assignment:** Sixty kittens were assigned to the study. Because of difficulty in obtaining kittens within the narrow age range, the study was conducted in two replicates, with 3/sex/group in each replicate. Unique randomization tables were generated for each replicate. On day -1 of each replicate, kittens meeting the inclusion criteria were separated by gender and ranked by day -1 body weights in descending order. A pre-generated table was then used to assign ranked kittens to one of the five treatment groups. The table consisted of pre-generated random numbers in sets of 5, by which the five heaviest kittens of one sex were each assigned to one of the five treatment groups, with the smallest number assigned to Group 1, the next smallest to Group 4, the next to Group 5, then to Group 3 and finally Group 2. This allocation process was continued for the remaining 5 sets of kittens. A littermate review was then conducted to ensure that the two 5X treatment groups (Groups 3 and 5) did not contain more than one male and one female from the same litter.

Table 1: Study design			
Group	Test Material Applied	Volume of each application	Cumulative amount applied on Day 0; also on Day 14
1	Mineral oil	1 st application = 0.35 mL; 2 nd & 3 rd = 0.4 mL	1.15 mL
2	Vehicle of proposed formulation (no active ingredients) at 3X	3 applications @ 0.21 mL	0.63 mL
3	Vehicle of proposed formulation (no active ingredients) at 5X	3 applications @ 0.35 mL	1.05 mL
4	Proposed formulation (with active ingredients) at 3X	3 applications @ 0.23 mL	0.69 mL
5	Proposed formulation (with active ingredients) at 5x	1 st app = 0.35 mL; 2 nd & 3 rd = 0.4 mL	1.15 mL

3. **Dose selection rationale:** According to a cover letter dated November 30, 2009 from the registrant the proposed product Advantage IGR 5 is "especially designed for small cats and kittens in a smaller single-use tube (0.23 mL)." This is consistent with the cumulative 3X dosage of 0.69 mL indicated above, as well as the cumulative 5X dosage of 1.15 mL.
4. **Application:** The test and control substances were topically applied using a calibrated pipette, with each dose split into 3 sub-applications at approximately 60-minute intervals. Application was directly to the skin on the dorsal midline from the base of the skull to the interscapular (between the shoulder blades) region.
5. **Statistics:** From p. 21 of MRID 47924801: "...The experimental unit was defined as the individual animal. Descriptive statistics (mean and standard deviation) were analyzed for all variables for all treatment groups... Statistical analyses were performed to further evaluate body weight, food consumption, and liver values (ALT, AST, ALP and GGT) for a potential treatment effect (using an alpha of 0.05). A repeated measures analysis of covariance including the classification terms 'treatment,' 'time,' and 'sex'; the two-way interactions 'treatment by time,' 'sex by time,' and 'treatment by sex'; the three-way interaction 'treatment by time

C. **METHODS:**

1. **Observations:**

- a. **Observations:** The animals were observed twice daily (morning and afternoon) except on days of treatment and on the first day following each dosage. On treatment days (0 and 14) kittens were observed pretreatment, and at 1, 2, 3 and 4 hours (\pm 15 minutes) following completion of the third and final sub-application. On days 1 and 15, kittens were observed at approximately 8:00 am, 11:00 am, and 3:00 pm (\pm 30 minutes).
- b. **Veterinary examinations:** Physical examinations were conducted by a veterinarian on days -7 -3, +1, +15 and +28. The examinations included but were not limited to heart rate, auscultation of the heart and lungs, mucous membranes, eyes, ears and genital organs.

2. **Body weight:** Animals were weighed on Days -7, -3, -1, +6, +13, +20 and +28.

3. **Food consumption:** Food consumption was "assessed" once daily between days -7 through termination (day 28). In addition to dry food (150 g offered/day), any kitten that exhibited inappetance and/or abnormal feces (loose stools or diarrhea) was offered moist food. The amounts of moist food offered and consumed were recorded in the raw data.

4. **Hematology and clinical chemistry:** Blood was collected for hematology and clinical chemistry assessments on unfasted kittens on the following days: -7, +1 (approximately 21 hours post-treatment), 15 (approximately 24 hours post-treatment), 19 (Group 5 kitten 08KPK1 only) and at termination on day 28. To avoid putting additional stress on the kittens, only 1 to 3 mL of blood/kitten was collected at each time, consequently, coagulation times were not determined. All whole blood and serum specimens were shipped with frozen ice packs. Hematology and chemistry analyses were conducted by Antech Diagnostics, Morrisville, NC 27560. The CHECKED (X) parameters were examined:

a. **Hematology**

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*	X	Heinz bodies (HBD)
	(Thromboplastin time)		
	(Fibrinogen)		
	(Prothrombin time)		

*Recommended for companion animals safety evaluation based on OPPTS 870.7200

b. **Clinical chemistry**

ELECTROLYTES		OTHER	
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus *		Total Cholesterol
X	Potassium* (K)	X	Globulins*
X	Sodium* (NA)	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes, eg., *)	X	Total bilirubin *
X	Alkaline phosphatase (AP)*	X	Total protein*
	Cholinesterase (ChE)		Triglycerides
X	Creatine phosphokinase (CK)		Albumin/Globulin ratio
	Lactic acid dehydrogenase (LDH)	X	Direct bilirubin*
X	Alanine aminotransferase (ALT/also SGPT)*		Indirect bilirubin
X	Aspartate aminotransferase (AST/also SGOT)*		BUN/Creatinine ratio
X	Gamma glutamyl transpeptidase (GGT)		TCO ₂ Bicarbonate
	Amylase		
	Sorbitol dehydrogenase		

* Recommended for a companion animal safety evaluation based on OPPTS 870.7200

5. **Urinalysis:** Urinalysis was not conducted.

6. **Sacrifice and pathology:** The study did not have a scheduled necropsy, and all kittens survived.

II. RESULTS

A. **DOSES ADMINISTERED ON A BODYWEIGHT BASIS:** The only kittens treated with the active ingredients were in Groups 4 (3X the proposed dosage treatment) and 5 (5X the proposed dosage treatment). The cumulative doses in these groups (0.69 mL at 3X, 1.15 mL at 5X) on days 0 and 14 remained the same. As all kittens gained weight between day -1 and 13, the dosages of active ingredients on a body weight basis decreased.

Group 4 (3X)	Table 2. Dosages for actives on a mg/kg basis			
	Day 0 (mg/kg)		Day 14 (mg/kg)	
	Pyriproxyfen	Imidacloprid	Pyriproxyfen	Imidacloprid
Minimum	3.999	75.725	2.770	52.452
Maximum	5.575	105.564	4.741	89.778
Mean	4.609	87.279	3.462	65.549
Group 5 (5X)	Day 0 (mg/kg)		Day 14 (mg/kg)	
	Pyriproxyfen	Imidacloprid	Pyriproxyfen	Imidacloprid
Minimum	5.848	110.744	4.177	79.092
Maximum	9.655	182.827	7.417	140.443
Mean	7.350	139.184	5.526	104.645

B. OBSERVATIONS:

1. **Cosmetic effects:** All kittens showed cosmetic hair coat effects (greasy, matted, and/or spike hair at dose site) at 1-4 hours post-dose on days 0 and 14, and in some cases these effects were noted on subsequent days, particularly in Group 1 (all 12 kittens on day 15, and 5 on day 16), with a few occurrences in Group 2 (two kittens on day 15 and one on day 16), Group 3 (two kittens on day 15 and one on day 16), and one in Group 5 (day 15 only). One Group 3 female had hair coat effects on day 21.
2. **Clinical signs of toxicity:** Loose stools and/or diarrhea occurred sporadically throughout the study in all groups. There seemed to be an increased incidence on days 14, 15 and 16 relative to days 12 and 13, but a closer examination of the data shows that days 5 and 6 also had reduced incidences. Since days 0 and 14 were Mondays, days 5-6 and 12-13 were weekends, and possibly the kittens were not observed as closely on those days as at other times; refer to Table 3, below:

Table 3. Occurrences of loose stools and diarrhea by group and sex on days 0 through 21.																						
Group & Sex	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1M	1L		2L	1L	1L			1L 1d	1L 1D	1L 1d		2D 2D			1L 1d		1L 1d				1D	1D
1F					1D	1D	1D	1D		1D	1D	1L 1d		1D	1L 1d	1D	1L				1D	1D
2M	1L			1L	1L										1L		1L	1L 1d			1L	1L
		1D	1D					1D								1D						1D
2F	1L				1L			2L 1d		1L	1L 1d				1L							
			2D	2D						1D	1D			1D	1D			1D	1D		1D	
3M	1L	1L 1d		1L	1L			1L				1L			1L	1L						
					1D										1D	1D		1D	1D		1D	
3F			1L						1L	1L							1L 1d					
							1D			1D	1D	1D										
4M		1L													1L	2L 1d	1L 1d					
				1D														2D	1D			
4F		2L	1L	2L				1L	2L	3L		1L			2L	2L	1L	1L				1L
					1D			1D	1D		2D	2D	2D							1D	1D	2D
5M					1L 1d				1L	1L		1L 1d										
				1D			1D	1D		1D	2D	1D			1D	2D	1D					
5F		1L 1d	1L	2L	1L			2L 1d	1L 1d	1L	1L				2L	1L	3L					3L
			1D	1D	2D	1D	1D			1D	1D	1D		1D		1D		2D	2D	1D	1D	
Total	4	7	9	12	12	2	4	14	9	14	14	13	3	2	15	14	13	11	5	2	7	10

Number = number of kittens with one or more occurrences on that day; L = loose stools; d = diarrhea with occurrence of loose stools for that kitten on same day; D = diarrhea without occurrence of loose stools.

On study day 15, kitten 08KPK1 (a male in Group 5) was observed to be lethargic. This kitten also showed abnormal feces (loose stools and/or diarrhea on days 11, 14 and 15) and had also shown intermittent anorexia (days 11 and 15) and a 3 g decrease in body weight (from 939 to 936 g) between days 6 and 13.

3. **Mortality:** All kittens survived to the end of the study.

B. BODY WEIGHT AND WEIGHT GAIN: Body weight data are presented in Table 3. All individual kittens gained weight from Day -1 to Day 28, although some individual kittens lost weight during some of the study intervals (Group 1 female 08QNM3 lost 33 g between days 13 and 20; Group 4 male 08QNM1 lost 45 g between days 13 and 20; Group 5 male 08KPK1 lost 3 g between days 13 and 20, and Group 5 female 08JNG3 lost 62 g between days 20 and 28). Mean body weight gains of Group 5 males and females were noticeably lower than those of the other groups in the period from Day -1 to Day 20 (which included applications on Days 0 and 14), and this was particularly pronounced in Group 5 females as their mean weight gains from Day -1 to 6 and from Day 13-20 (the test material was applied at 5X on Days 0 and 14) were considerably lower than the means from other females of the other groups.

Group & Sex	Table 4. Mean body weights (kg)					
	Day -7	Day -1	Day 6	Day 13	Day 20	Day 28
1 M	0.712	0.841	1.010	1.166	1.348	1.581
2 M	0.734	0.851	1.016	1.176	1.375	1.588
3 M	0.727	0.845	1.003	1.157	1.310	1.518
4 M	0.696	0.825	1.002	1.134	1.336	1.563
5 M	0.750	0.863	1.020	1.151	1.304	1.524
1 F	0.627	0.739	0.883	0.990	1.142	1.317
2 F	0.643	0.758	0.913	1.035	1.163	1.358
3 F	0.629	0.742	0.897	1.022	1.201	1.353
4 F	0.619	0.731	0.861	0.963	1.148	1.299
5 F	0.664	0.772	0.876	1.039	1.145	1.263

Group & Sex	Table 5. Mean body weight gains (kg)						
	Day -7 to Day -1	Day -1 to Day 28	Day -1 to Day 20	Day -1 to Day 6	Day 6 to Day 13	Day 13 to Day 20	Day 20 to Day 28
1 M	0.129	0.740	0.507	0.169	0.156	0.182	0.233
2 M	0.117	0.737	0.524	0.165	0.160	0.199	0.213
3 M	0.118	0.673	0.465	0.158	0.154	0.153	0.208
4 M	0.129	0.738	0.511	0.177	0.132	0.202	0.227
5 M	0.113	0.661	0.441	0.157	0.131	0.153	0.220
1 F	0.112	0.578	0.403	0.144	0.107	0.152	0.175
2 F	0.115	0.600	0.405	0.155	0.122	0.128	0.195
3 F	0.113	0.611	0.459	0.155	0.125	0.179	0.152
4 F	0.112	0.568	0.417	0.130	0.102	0.185	0.151
5 F	0.108	0.491	0.373	0.104	0.163	0.106	0.118

C. FOOD CONSUMPTION: No treatment-related effects were reported or are evident from group or individual data (refer to Table 5.3, pages 182-184 of MRID 47924801). From p. 19: "Food consumption was assessed once daily between days -7 through termination (day 28)." According to the text on p. 23: "Although slight decreases in food consumption were recorded for several animals in all treatment groups on the day of treatment and/or the initial 2-3 days post-treatment, food consumption gradually increased, as expected for growing kittens, over the course of this study."

From p. 19: "In addition to dry food, any kitten that exhibited inappetance and/or abnormal feces (i.e., loose or diarrhea) was offered moist food." The following is from p. 24:

*Moist Food Offered During the Exposure Period				
Animal ID (Sex)	Group	Treatment	Timepoint(s) (when moist food offered)	Amount of Moist Food Offered per Timepoint (g)
08KPV3 (M)	1	0X (Control/Reference)	Days 10, 11	20, 20
08QNM3 (F)	1	0X (Control/Reference)	Days 17, 18	20, 20
08KPG5 (F)	1	0X (Control/Reference)	Days 17, 18	20, 20
08QNP3 (F)	2	3X (Vehicle Substance)	Days 10, 11, 17	20, 20, 20
08KPK4 (F)	2	3X (Vehicle Substance)	Days 17, 18	20, 20
08KPV4 (F)	3	5X (Vehicle Substance)	Days 10, 11	20, 20
08QN2 (M)	3	5X (Vehicle Substance)	Days 17, 18	20, 20
08KPW6 (F)	3	5X (Vehicle Substance)	Day 25	20
08QNP4 (F)	4	3X (Test Substance)	Days 10, 11, 23, 24	20, 20, 20, 20
08QNM1 (M)	4	3X (Test Substance)	Days 17, 18	20, 20
08KPY2 (F)	4	3X (Test Substance)	Day 22	20
08KPI8 (F)	4	3X (Test Substance)	Days 22, 24	20, 20
08KPZ1 (M)	5	5X (Test Substance)	Days 10, 11	20, 20
08KPW2 (M)	5	5X (Test Substance)	Days 10, 11	20, 20
08KPW8 (F)	5	5X (Test Substance)	Days 10, 11, 23, 24, 25	20, 20, 20, 20, 20
08KPK1 (M)	5	5X (Test Substance)	Days 15, 16, 17, 18	75, 75, 20, 20
08QNR4 (F)	5	5X (Test Substance)	Day 22	20
08KQA7 (F)	5	5X (Test Substance)	Days 22, 23, 24, 25	20, 20, 20, 20
08JNG3 (F)	5	5X (Test Substance)	Days 24, 25	20, 20

*Table from p. 24 of MRID 47924801.

According to the protocol (see page 40 of MRID 47924801): "Kittens exhibiting inappetance may be offered moist food" with no mention of loose stool and/or diarrhea. It appears that the decision to provide moist food to kittens with diarrhea and/or loose stools may have been made about day 10. Seven kittens were given moist food on day 10, although 13 showed loose stool and/or diarrhea on that date.

Since individual food consumption values (in g/kitten/day) are reported in MRID 47924801 on a weekly (rather than daily) basis, TRB requested and received individual daily food consumption data.

From the individual food consumption data, there is no indication that exposure to the test material (or the control reference or vehicle substance) on day 0 resulted in a decrease in food consumption. One control reference (Group 1) male kitten (08KPF3) is reported to have consumed 114 g on Day 0. One Group 5 female (08KPI6) consumed only 20 g on Day 1, but this animal had consumed only an average of 32 g/day from Day -7 to -1. On Day 14 (second treatment) Group 5 male consumed only 6 grams, and then only 20 grams on Day 15; this kitten was then offered (in addition to the usual ration) 75 g of moist food on Days 16 and 17, and consumed 84 and 81 g of food on those days, respectively.

D. CLINICAL PATHOLOGY ANALYSES:

1. **Hematology:** No treatment-related changes were observed in any of the parameters. On Day 15 (refer to p. 25 and p.p. 114-115 of MRID 47924801), group 5 kitten 08KPK1 had an increased percentage (82.5) of neutrophils, an increased percentage (37.72) of absolute neutrophils, with elevated percentages of basophils and absolute basophils (2.2 and 1.2, respectively). This is suggestive of a response to a bacterial infection.

2. **Clinical Chemistry:** No treatment-related changes were observed in any of the parameters. On Day 15 (refer to p. 26 and p. 141-142 of MRID 47924801, group 5 male 08KPK1 had a high BUN (105 mg/dL), normal creatinine, low sodium and low chloride, elevated potassium, elevated total protein and slightly elevated glucose. From p. 26: "The observed hematology and serum chemistry changes were likely secondary to dehydration. Decreased sodium and chloride values may also be secondary to hyperproteinemia..." An elevated BUN >60 mg/dL with a normal creatinine level suggests a moderate-to-severe degree of acute renal failure. This kitten had loose stool and diarrhea on days 11, 14 and 15. Blood was taken from this kitten on day 19 and hematology and clinical chemistry parameters were measured (see p. 149); by day 19 the BUN (36 mg/dL), sodium, chloride and potassium levels were within normal reference ranges.

III. DISCUSSION AND CONCLUSIONS

- A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that no treatment-related clinical signs or effects on the variables measured were observed in kittens 8 weeks of age and older and/or up to 5 pounds treated topically, biweekly for two consecutive treatments with 0, 3, or 5 times the label dose of the imidacloprid + pyriproxyfen spot-on.
- B. **REVIEWER COMMENTS:** All animals survived to the end of the study. There were no indications of dose-related signs at the 3x dose level. Possible indications of systemic toxicity at the 5x dose level included the lethargy seen in male 08KPK1 (while this kitten was reported to have had pre- and post-dose diarrhea on day 14, as well as diarrhea on day 15, and had clinical chemistry results from day 15 that suggested electrolyte loss and dehydration – consistent with the diarrhea – the possibility that treatment and/or exposure to the test material on day 14 exacerbated its condition cannot be discounted). In addition, mean body weight gains in Group 5 males and females in the period from day -1 to 20 were lower than the corresponding values from other groups, and this was particularly pronounced in Group 5 females for weeks the test material was applied (Days -1 to 6 and 13-20).

It is concluded that the margin of safety in kittens administered topical application of M880 Insecticide (9.1% imidacloprid and 0.46% pyriproxyfen) was at least 3X. According to the OPPTS 870.7200 Companion Animal Safety Test Guidelines the targeted adequate margin of safety is 5X, but consideration can be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life threatening signs). In this case, the possible (but ambiguous) signs of toxicity observed at 5X were limited to lethargy in one kitten following treatment on Day 14, and lower weight gains in the test group (particularly females, which showed reduced weight gains for the weeks in which they were treated with the test material).

This study is acceptable and can be used to support the proposed use of M880 Insecticide (9.1% imidacloprid and 0.46% pyriproxyfen) on kittens 8 weeks old and older at a dosage rate of 0.23 mL/application, with retreatment no more often than once every 14 days.

1. **DP BARCODE:** 372322
2. **PC CODES:** 129099 (Imidacloprid); 129032 (Pyriproxyfen)
3. **CURRENT DATE:** April 15, 2010
4. **TEST MATERIALS:** Controls (Group 1): Mineral Oil; Vehicle Controls (Groups 2 & 3):
Test material without active ingredients; M880 Insecticide (Groups 4 & 5): Bayer
Imidacloprid/Pyriproxyfen Dog/Cat Spot On containing 9.1% Imidacloprid and 0.46%
Pyriproxyfen.

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Companion Animal Safety Study/Kittens Sinclair Research, Auxvasse, MO 65231 Bayer Animal Health Study No. 152.141 / October 9, 2009.	47924801	Five groups (each 6M & 6F) of 8 week old kittens were treated on Days 0 & 14. Group 1 was treated with a total of 1.15 mL mineral oil; Group 2 with a total of 0.63 mL formulation vehicle; Group 3 with 1.05 mL formulation vehicle; Group 4 with 3X (=0.69 mL) proposed formulation; Group 5 with 5X (=1.15 mL) proposed formulation. Possible (but ambiguous) signs of toxicity at 5X were lethargy in one kitten following day 14 application, and reduced mean weight gains, particularly in females on weeks of treatment.	N/A	A

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived

CHILD-RESISTANT PACKAGING REVIEW
Technical Review Branch

IN 12/15/2009

OUT 2/17/2010

RD, TRB, Reviewed by Rosalind L. Gross

Rosalind L. Gross
2/17/2010

EPA Reg. No. or File Symbol 11556-RLN, 11556-RLR, 11556-RLE

DP Barcode D372321, 372324, 372323

Decision # 424201, 424200, 424199

EPA Petition or EUP No. _____

Date Division Received 12/03/2009

Type Product(s) Insecticide (flea product)

Data Accession No(s). 479248-02 & 03, 479252-01, 02, 03, & 04, 479249-01, 02, 03, & 04

Product Mgr./Chemical Review Mgr/Contact Person RM 01 (Kable Davis)

Division RD

Product Name(s) Advantage IGR 5, Advantage IGR 9, Advantage IGR 18

Company Name(s) Bayer Healthcare LLC

Submission Purpose Review of CRP studies to determine if they are adequate to support CRP certification for retail blisters of nonchild-resistant tubes.

Active Ingredient(s), PC code, & % Imidacloprid 9.1%

Pyriproxyfen 0.46%

Summary of Findings

The CRP certifications submitted November 30, 2009 for EPA Registration No. 11556-RLN, 11556-RLR, and 11556-RLE are acceptable. A screening of CRP studies (MRID numbers 479248-02 & 03, 479252-01, 02, 03, & 04, 479249-01, 02, 03, & 04) revealed the CRP studies associated with the lowest senior adult use effectiveness (SAUE) was MRID number 479248-03 and the lowest child-resistant effectiveness (CRE) was MRID number 479252-03. A comprehensive review was done for the lowest SAUE including the CRE associated with it (MRID numbers 479248-03 & 479248-02) and the lowest CRE including the SAUE associated with it (MRID numbers 479252-03 & 479252-04). The results of the comprehensive review for MRID numbers 479248-03 & 479248-02 and 479252-03 & 479252-04 indicate these studies pass the CRE sequential test chart and SAUE requirements in 16 CFR 1700.20.

For the details of each study refer to the attached summary chart (summarycht11556-150,151,152.doc).

Based on the CRE and SAUE values the registrant reported for MRID numbers 479252-01 & 02, 479249-01, 02, 03, & 04 along with a computerized analysis of the data these studies pass the CRE sequential test chart and SAUE requirements in 16 CFR 1700.20. **For the details of each study refer to the attached summary chart (summarycht11556-150,151,152.doc).**

In conclusion all the requirements for CRP have been met for EPA Reg. No. 11556-RLN, 11556-RLR, and 11556-RLE. However, the directions on opening the package given to consumers must be identical to those given to the seniors during testing for the blisters. The senior testing directions are on the labels for EPA Reg. No. 11556-RLN, 11556-RLR, and 11556-RLE dated November 24, 2009. Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the child resistance of the package involved.

Package

The package is a plastic blister with a foil backing containing tubes of product, which the registrant refers to as a tropical foil KISI blister. The blister is the child-resistant packaging, CRP, not the individual tubes.

Toxicity

The toxicity of the product, which contains 9.1% Imidacloprid and 0.46% Pyriproxyfen, is based on toxicity data for a 9.0% Imidacloprid and 0.48% Pyriproxyfen formulation. The acute oral LD₅₀ study MRID 470894-11 (9.0% Imidacloprid and 0.48% Pyriproxyfen) is 1098mg/kg for the female rat, no male rat was used in the study. The toxic or harmful amount for an 11.4 kg child is 12.5g (1098mg/kg x 11.4kg), which is 11.4ml of product (12.5g divided by 1.092g/ml [product density]).

Failure

For the purposes of CRP testing a **child failure** is access to 12.5g = 11.4ml or 9 blister cavities, whichever is less. A **blister cavity failure for the child test** was defined as any breach/penetration of the blister cavity, a visible incision or opening made by a child, or any amount of placebo/water accessed.

A **Senior Adult Use Effectiveness failure** is failure to open the blister cavity in the prescribed test time of 5 minutes for the first package or 1 minute for the second package, cutting the tube while opening the blister cavity for either the first or second package, or accessing any amount of placebo/water while opening the blister cavity for either the first or second package.

Toxicity, Child Failure, and Package

Package Size	Toxic/Harmful Amt	Child Failure
4 tubes @ 0.23ml	50 tubes	9 tubes
4 tubes @0.4ml	29 tubes	9 tubes
6 tubes @0.4ml	29 tubes	9 tubes
4 tubes @0.8ml	15 tubes	9 tubes
6 tubes @0.8ml	15 tubes	9 tubes

Analysis of Data and Conclusion

The CRP certifications submitted November 30, 2009 for EPA Registration No. 11556-RLN, 11556-RLR, and 11556-RLE are acceptable. A screening of CRP studies (MRID numbers 479248-02 & 03, 479252-01, 02, 03, & 04, 479249-01, 02, 03, & 04) revealed the CRP studies associated with the lowest senior adult use effectiveness (SAUE) was MRID number 479248-03 and the lowest child-resistant effectiveness (CRE) was MRID number 479252-03. A **comprehensive** review was done for the lowest SAUE including the CRE associated with it (MRID numbers 479248-03 & 479248-02) and the lowest CRE including the SAUE associated with it (MRID numbers 479252-03 & 479252-04).

Child Study 4 turquoise tube blister 0.23 ml size (MRID 479248-02) involved giving each child 3 blister cards with 4 tubes each containing 0.23 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. A test date was missing, but was in the hard copy and the subject's age was correctly reported. The results were no child failures, but 2 children accessed 2 blister cavities each. **This study was a pass according to the child sequential test in 16 CFR 1700.20.**

Senior Adult Use Effectiveness Study 4 turquoise tube blister 0.23 ml size (MRID 479248-03 which is the lowest SAUE) involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for their use. There were two age calculation errors in the study. A 62 year old female was reported as 61 years old and a 61 year old male was reported as 62 years old. However, the subjects remained in the same age group and the age and sex distribution remain acceptable. The results of the study were 97% SAUE. **The study is a pass of the Senior Adult test in 16 CFR 1700.20.**

Child Study 6 orange tube blister 0.4 ml size (MRID 479252-03 which is the lowest CRE) involved giving each child 2 blister cards with 6 tubes each containing 0.4 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. Ten children accessed one or more blister cavities. 3 children accessed 1 blister cavity, 2 children accessed 2

blister cavities, 3 children accessed 3 blister cavities, one child accessed 7 blister cavities, one 51 month female child accessed 9 blister cavities (failure). The results were one child failure. This study was a pass according to the child sequential test in 16 CFR 1700.20.

Senior Adult Use Effectiveness Study 6 orange tube blister 0.4 ml size (MRID 479252-04) involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for their use. The results of the study were 99% SAUE, a 65 year old female failed during the five minute test period. The study is a pass of the Senior Adult test in 16 CFR 1700.20.

Based on the CRE and SAUE values the registrant reported for MRID numbers 479252-01 & 02, 479249-01, 02, 03, & 04 along with a computerized analysis of the data these studies pass the CRE sequential test chart and SAUE requirements in 16 CFR 1700.20. For the details of each study refer to the attached summary chart (summarycht11556-150,151,152.doc).

In conclusion all the requirements for CRP have been met for EPA Reg. No. 11556-RLN, 11556-RLR, and 11556-RLE. However, the directions on opening the package given to consumers must be identical to those given to the seniors during testing for the blisters. The senior testing directions are on the labels for EPA Reg. No. 11556-RLN, 11556-RLR, and 11556-RLE dated November 24, 2009. Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the child resistance of the package involved.

CRPdatasummarycht

Chemical - Pyriproxyfen 0.46%
Imidacloprid 9.1%

Company Name Bayer Healthcare LLC

A Senior Adult Use Effectiveness failure is failure to open the blister cavity in the prescribed test time of 5 min. for the 1st pkg or 1 min. for the 2nd pkg, cutting the tube while opening the blister cavity for either the 1st or 2nd pkg, or accessing any amount of placebo/water while opening the blister cavity for either the 1st or 2nd pkg.

A child failure is access to 12.5g = 11.4ml for Product Density 1.092g/ml or 9 tubes, whichever is less

A blister cavity failure is any breach/penetration of the blister cavity, a visible incision or opening made by a child, or any amount of placebo/water accessed.

Access to a toxic or harmful amt = 12.5g = 1.098g/kg x 11.4kg (MRID 470894-11 oral LD₅₀) = 11.4ml for Product Density 1.092g/ml

% AI - Pyriproxyfen 0.46%

Imidacloprid 9.1%

EPA REG #	MRID	PKG Description Include ml per Pkg Blister is CR feature not tube.	# Pkges	Company Data		Data		Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity = bc	SAUE	Comprehensive Review & why	Only Computer Analysis	include CRE & SAUE via computer analysis
11556-RLN (556-150)	479248-03 cat product	4 turquoise tube @ 0.23ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 50 tubes, child fail = 9 tubes			97% 3 fail pkg A open (2 cut tube)	X lowest SAUE & smest size		CRP Certification is ok. Label dated 11/24/09 same CRP directions as In study. Data Analysis showed 2 age calcn errors [a 62 yr old female was reported as 61 yrs old and a 61 yr old male was reported as 62 yrs old]. However the subjects remained in the same age grp, the age & sex distribution remains ok. Results are not affected. SAUE is 97%, study is a pass.

EPA REG #	MRID	PKG Description include ml per Pkg Blister is CR feature not tube.	# Pkgs	Company Data		Data		Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity = bc	SAUE	Comprehensive Review & why	Only Computer Analysis	include CRE & SAUE via computer analysis
11556-RLN (11556-150)	479248-02 cat product	4 turquoise tube @ 0.23ml in tropical foil (KISi) blister. Water placebo in tube. Tox/harm = 50 tubes, child fail = 9 tubes	3 blisters with 4 tubes each	0 Fail = Pass 50 child test. 2 child open 2 bc each		X CRE associated with lowest SAUE & smest size ml		CRP Certification is ok. A test date was missing, but was in hard copy & subject age was correctly reported. 2 child open 2 bc each. No child failures. Study is a pass of the child test according to sequential test chart in 16 CFR 1700.20.
11556-RLR (11556-151)	479252-02 cat product	4 orange tube @ 0.4ml in tropical foil (KISi) blister. Water placebo in tube. Tox/harm = 29 tubes, child fail = 9 tubes			97% 3 fail pkg A open (1 cut tube tip)		X	CRP Certification is ok. Label dated 11/24/09 same CRP directions as in study. Data Analysis showed 1 age calcn error, a 67 yr old female was reported as 57 yrs old. The age group & sex distribution are off, which means there are more older test subjects & more than 70%female in the 60-70 yr age grp. The results are still a pass of the SAUE in 16 CFR 1700.20.

EPA REG #	MRID	PKG Description Include ml per Pkg Blister is CR feature not tube.	# Pkges	Company Data		Data		Conclusion
				CRE blister cavity = bc	SAUE	Comprehensive Review & why	Only Computer Analysis	
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test					include CRE & SAUE via computer analysis
11556-RLR (11556-151)	479252-01 cat product	4 orange tube @ 0.4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 29 tubes, child fail = 9 tubes	3 blisters with 4 tubes each	0 Fail = Pass 50 child test. 6 children open \geq 1bc. 4 children open 1bc, 1child open 3 bc, 1child open 4 bc			X	CRP Certification is ok. Data Analysis showed 1 age calcn error, a 50 month old male was reported as 51 months old. However the subject remained in the same age grp, the age & sex distribution remains ok. 6 children open \geq 1bc. 4 children open 1bc, 1child open 3 bc, 1child open 4 bc. No child failures. Study is a pass of the child test according to sequential test chart in 16 CFR 1700.20.
11556-RLR (11556-151)	479252-04 cat product	6 orange tube @ 0.4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 29 tubes, child fail = 9 tubes			99% 1 fail pkg A open (no open tube)	X SAUE associated with lowest CRE		CRP Certification is ok. Label dated 11/24/09 same CRP directions as in study. SAUE is 99%, a 65 yr old female failed in the 5 min test period. The study is a pass.

EPA REG #	MRID	PKG Description Include ml per Pkg Blister is CR feature not tube.	# Pkges	Company Data		Data		Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity = bc	SAUE	Comprehensive Review & why	Only Computer Analysis	include CRE & SAUE via computer analysis
11556-RLR (11556-151)	479252-03 cat product	6 orange tube @ 0.4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 29 tubes, child fail = 9 tubes	2 blisters with 6 tubes each	1 Fail = Pass 50 child test. 10 children open \geq 1bc. 3 children open 1bc, 2 children open 2bc, 3 children open 3bc, one child open 7 bc, one child open 9 bc (failure).		X lowest CRE		CRP Certification is ok. 10 children open \geq 1bc. 3 children open 1bc, 2 children open 2bc, 3 children open 3bc, one child open 7 bc, one 51 month female child open 9 bc (failure). There is one child failure. Study is a pass of the child test according to sequential test chart in 16 CFR 1700.20.
11556-RLE (11556-152)	479249-02 cat product	4 purple tube @ 0.8ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 15 tubes, child fail = 9 tubes			98% 1 fail pkg A open (cut into side of tube) and 1 fail pkg B open in 60 sec		X	CRP Certification is ok. Label dated 11/24/09 same CRP directions as in study. Data Analysis showed 1 age calcn error, a 61 yr old female was reported as 62 yrs old. However the subject remained in the same age grp, the age & sex distribution remains ok. Results are not affected. SAUE is 98%, study is a pass.

EPA REG #	MRID	PKG Description Include ml per Pkg Blister is CR feature not tube.	# Pkges	Company Data		Data		Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity = bc	SAUE	Comprehensive Review & why	Only Computer Analysis	include CRE & SAUE via computer analysis
11556-RLE (11556-152)	479249-01 cat product	4 purple tube @ 0.8ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 15 tubes, child fail = 9 tubes	3 blisters with 4 tubes each	0 Fail = Pass 50 child test. 5 children open 1bc			X	CRP Certification is ok. Data Analysis showed 3 age calcn errors, [a 44 month old male was reported as 43 months old, a 46 month old female was reported as 47 months old, a 49 month old female was reported as 50 months old]. However the subjects remained in the same age grp, the age & sex distribution remains ok. 5 children open 1bc. No child failures. Study is a pass of the child test according to sequential test chart in 16 CFR 1700.20.
11556-RLE (11556-152)	479249-04 cat product	6 purple tube @ 0.8ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 15 tubes, child fail = 9 tubes			99% 1 fail pkg A open (cut tip off tube)		X	CRP Certification is ok. Label dated 11/24/09 same CRP directions as in study. SAUE is 99%, study is a pass.

EPA REG #	MRID	PKG Description Include ml per Pkg Blister is CR feature not tube.	# Pkges	Company Data		Data		Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity = bc	SAUE	Comprehensive Review & why	Only Computer Analysis	include CRE & SAUE via computer analysis
11556-RLE (11556-152)	479249-03 cal product	6 purple tube @ 0.8ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 15 tubes, child fail = 9 tubes	2 blisters with 6 tubes each	0 Fail = Pass 50 child test. 11 children open \geq 1bc. 5 children open 1 bc, 3 children open 3 bc, 2 children open 4 bc, one child open 6 bc.			X	CRP Certification is ok. Data Analysis showed 1 age calcn error, a 43 month old male was reported as 42 months old. However the subject remained in the same age grp, the age & sex distribution remains ok. 11 children open \geq 1bc. 5 children open 1 bc, 3 children open 3 bc, 2 children open 4 bc, one child open 6 bc. No child failures. Study is a pass of the child test according to sequential test chart in 16 CFR 1700.20.

February 17, 2010

Bayer HealthCare
Animal Health



Via Federal Express

November 30, 2009

Document Processing Desk (NO REGFEE – Additional Information)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Attention: Ms. Venus Eagle (PM01)
Registration Division

Subject: Advantage[®] IGR 5 (File Symbol No. 11556-XXX)
Child-Resistant Packaging Certification

RLW

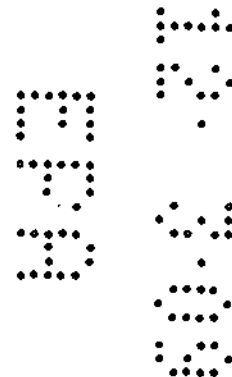
Dear Ms. Eagle:

I certify that the packaging that will be used for this product meets the standard of 40 CFR 157.32.

Sincerely,

Douglas A. Spilker, Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker.b@Bayer.com

DAS/lt





Bayer HealthCare
Animal Health

Via Federal Express

November 30, 2009

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle
Registration Division

Subject: Applications for the Registration of
Advantage[®] IGR 5 (Agency Tracking #74089836606),
Advantage[®] IGR 9 (Agency Tracking #74089836904), and
Advantage[®] IGR 18 (Agency Tracking #74089837114)
products for pest control on cats and kittens

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Ms. Eagle:

Enclosed with this cover letter are applications for registration of three (3) new companion animal spot-on products, named *Advantage IGR 5*, *Advantage IGR 9*, and *Advantage IGR 18*, and all the appropriate supporting documents and data. These imidacloprid + pyriproxyfen-containing products will be packaged in single-use tubes for application by pet owners and veterinarians for control of various stages of fleas and lice on cats and kittens. The purpose of this cover letter is to provide an explanatory overview of the submission which may aid in the processing of the enclosed information and respective registration applications.

Although these are applications for registration of *new* products, the products themselves are not really new to the Agency. On December 11, 2007, the Agency issued Notices of Registration for both *Advantage Plus 9 for Cats* (EPA Reg. No. 11556-126) and *Advantage Plus 18 for Cats* (EPA Reg. No. 11556-129). The proposed three products contain the identical formulation and use pattern, residential - indoor, as the previously accepted products of Advantage Plus 9 and 18. Although Bayer

HealthCare subsequently voluntarily withdrew the registrations of *Advantage Plus 9* and *Advantage Plus 18*, this was for marketing reasons, and not because of a safety/risk issue or lack of data for the products. Therefore, much of the data needed to support these proposed products have already been reviewed and accepted by the Agency during the review process for the *Advantage Plus 9* and *18*. Furthermore, there are analogous registrations for this identical formulation for use on dogs and puppies, currently registered as *Advantage Plus 10* (EPA Reg. No. 11556-128), *Advantage Plus 20* (11556-125) *Advantage Plus 55* (11556-127) and *Advantage Plus 100* (11556-130).

Applications for three (3) new products are enclosed and include *Advantage IGR 9* (0.4 mL tube), *Advantage IGR 18* (0.8 mL tube) and a third product, *Advantage IGR 5*, especially designed for small cats and kittens in a smaller single-use tube (0.23 mL). These products only differ from one another in terms of different dose/container sizes for different sizes of cats and kittens (see Table 1.)

Product Chemistry: The insecticide formulation is identical for all three of the proposed products, and is identical to the formulation previously accepted for the imidacloprid + pyriproxyfen-containing cat products (*Advantage Plus 9* and *18*), as well as the currently registered dog spot-on products (*Advantage Plus 10*, *20*, *55* and *100*). Therefore, the product chemistry data requirements have already been satisfied for this formulation. Appropriate Confidential Statements of Formula for the three proposed products are enclosed.

Efficacy: All of the products control fleas. These products are similar to the imidacloprid-containing *Advantage* products (*Advantage 9 Topical Solution*, EPA Reg. No. 11556-116; *Advantage 18 Topical Solution*, EPA Reg. No. 11556-118), except a small amount (0.46%) of a very effective insect growth regulator, pyriproxyfen, has been added to enhance efficacy against flea eggs. Whereas *Advantage* was efficacious against larval and adult fleas, the new combination product is effective against flea larvae, adult fleas, and flea eggs. Since the data, as listed in the data matrix, to support the flea control claims for this formulation have been reviewed and accepted by the Agency under the previous *Advantage Plus 9* and *Advantage Plus 18* actions, no new flea efficacy data are being submitted with this application. You will also note that the proposed labels contain many of the flea control claims found on the stamped-accepted labels for

Advantage Plus 9, Advantage Plus 18, as well as, on the stamped-accepted labels for *Advantage Plus 10, Plus 20, Plus 55 and Plus 100 for Dogs*.

The only other pest that appears on the proposed labels is the biting (chewing) louse. To support these claims, we reference the efficacy data previously submitted for lice control under the *Advantage Plus for Dogs* product, which is referenced in the Data Matrix.

Application Method and Weight Bands: The method of application is the same for all three products, and it is the same application method as for the currently registered *Advantage Topical Solution* products. The entire contents of the appropriate-sized tube are applied to cats or kittens to a localized area on the neck at the base of the skull to control fleas. One product, *Advantage IGR 5*, will treat cats and kittens weighing 5 lbs. or less in size. The dose for this product is 0.23 mL of solution in a plastic tube. The second product - *Advantage IGR 9* - will treat cats and kittens weighing 5 to 9 lbs. with a tube size of 0.4 mL. The third product - *Advantage IGR 18* - will treat cats weighing 9 lbs. and greater in size, with a tube size of 0.8 mL of solution in a plastic tube. All three tubes have different label colors to easily distinguish them from one another.

Acute Toxicity Studies: As discussed earlier, the insecticide formulation is the same for all three proposed products (and the currently registered dog products). We are relying on the previously accepted acute toxicity studies on the formulation to support these proposed registration actions; that is no new acute toxicity data are included with the applications. The Precautionary label language and Signal Word are the same as the currently EPA-accepted *Advantage Plus for Dog* products. Because the acute oral toxicity value for the formulation was below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP).

Packaging: The packaging for the proposed cat products will be identical to the packaging used with the currently registered *Advantage* products for cats (EPA Reg. Nos. 11556-116 and -118) except that the tubes will be in a Child-Resistant blister. The packaging for the cat products will consist of a cardboard box with all appropriate label text except for the full directions for use. Inside the box will be a leaflet containing all the label text. Also inside the box will be a CRP blister package containing 4 or 6 tubes of the appropriate size.

The most significant difference in the packaging between the previously registered products - *Advantage Plus 9* and *Advantage Plus 18* - and the proposed products is that the products are in a different Child-Resistant Packaging (CRP) material. For the previous products, the CRP packaging was made of PVC and the respective child and adult testing data were found acceptable to the Agency. The proposed products will be produced in KISI blisters. The packaging material scheme for all three of the proposed registrations is similar, and the CRP testing data for the various sizes are enclosed. The testing design to satisfy the requirements for all product presentations was developed with the agreement of the Agency's expert, Dr. Rosalind Gross. CRP certification letters are also enclosed.

With regard to the overall CRP testing of the various packaging configurations, Bayer is aware of PR Notice 97-9 regarding the electronic submission of CRP test data, and therefore these data have been prepared appropriately and are included on CDs.

Companion Animal Safety: Submitted in support of the previously accepted registrations for *Advantage Plus 9* for Cats and Kittens (EPA Reg. No. 11556-126) and for *Advantage Plus 18* for Cats (EPA Reg. No. 11556-129), Bayer has an appropriate domestic animal safety study on file with the Agency that demonstrates the safety of *Advantage IGR* on adult cats. The EPA concluded that the report was "Acceptable" and that the study adequately addressed the safety requirements contained in Guideline 870.7200: *Companion Animal Safety*. Furthermore, the study supports a 7-day retreatment interval. To support a label allowing treatment of 8-week old kittens, enclosed is a new domestic animal safety study (Bayer Report No. 33714) conducted using a protocol submitted to and accepted by the Agency.

Data Compensation: An appropriate data matrix listing all of the data necessary to support the registration of *Advantage IGR 5*, *Advantage IGR 9* and *Advantage IGR 18* is enclosed with this application. Please note, the enclosed data matrix cites only those data necessary for this registration. This registration application is for a product used only on cats (classified as an indoor, residential use); the data matrix does not cite any imidacloprid environmental fate, ecological effects nor residue chemistry data because these data are not necessary for this proposed registration.

Generic Data -With regard to **imidacloprid**, Bayer CropScience LP (BCS) is the basic registrant of imidacloprid. BCS and Bayer HealthCare

Ms. Venus Eagle
Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency

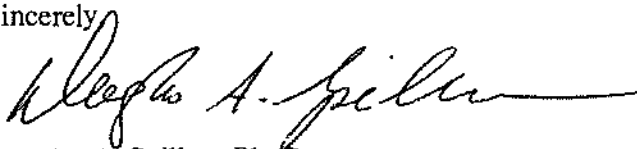
Page 5
November 30, 2009

LLC (BHC) are wholly owned subsidiaries of Bayer Corporation, and therefore, the BHC, Animal Health Division, cannot claim Formulator's Exemption for the generic data requirements. Accordingly, enclosed are copies of a Letter of Authorization from Bayer CropScience (EPA Company No. 264) authorizing the use of the generic imidacloprid data by Bayer HealthCare LLC, Animal Health Division (EPA Company No. 11556). These generic data are cited in the enclosed data matrix. With regard to **pyriproxyfen**, a completed Formulator's Exemption form (EPA Form 8570-27) is enclosed with this initial application for Bayer to address compensation of pyriproxyfen generic data. Also, enclosed is a Letter of Authorization from Sumitomo Chemical Company Ltd.

Product Specific Data - All of the data necessary to support the registration of *Advantage IGR 5*, *Advantage IGR 9* and *Advantage IGR 18* are data previously submitted by Bayer's Animal Health group (EPA Company No. 11556) or are enclosed with this application or were submitted by the McLaughlin Gormley King Co. (MGK). Enclosed with this application is a Letter of Authorization from MGK. All of these data are cited in the enclosed data matrix. Enclosed is also a completed Certification with Respect to Citation of Data (EPA Form 8570-34) indicating we are choosing the Selective Method of Support for pyriproxyfen efficacy data. Again, a Letter of Authorization from MGK to cite these data is enclosed.

I hope this overview cover letter is helpful in processing the attached applications. If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely,



Douglas A. Spilker, Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker.b@Bayer.com

DAS/lt

Enclosures

Table 1.

Product Name	Animal	Animal Size	Tube Size (fl. oz.)	No. of Tubes Per Package
Advantage [®] IGR 5 (EPA File Symbol 11556-XXX)	Cats and Kittens	≤ 5 lbs.	0.0078 (0.23 mL)	4
Advantage [®] IGR 9 (EPA File Symbol 11556-XXX)	Cats and Kittens	5 to 9 lbs.	0.014 (0.4 mL)	4 or 6
Advantage [®] IGR 18 (EPA File Symbol 11556-XXX)	Cats and Kittens	≥ 9 lbs.	0.027 (0.8 mL)	4 or 6

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Enclosures:

Advantage IGR 5

- 1 copy Advantage IGR 5 Application for Pesticide Registration with Application Attachment and five Appendices:
 - Appendix 1 – Advantage Plus 9 and 18 Registration Notices & Voluntary Cancellations
 - Appendix 2 – Product Chemistry Review
 - Appendix 3 – Storage Stability Extension and Interim Report
 - Appendix 4 – Acute Toxicity Study Reviews
 - Appendix 5 – CRP Correspondence
 - Appendix 6 – Lice Study Review
 - Appendix 7 – Companion Animal Safety Study Review
 - Appendix 8 – Companion Animal (kitten) Protocol Review
- 1 copy proof of PRIA payment
- 5 copies draft labels, date of draft 11/24/09
- 1 copy Letter of Authorization from MGK
- 1 copy Letter of Authorization from Bayer CropScience
- 1 copy Letter of Authorization from Sumitomo
- 1 copy CRP Certification letter
- 1 copy Formulator's Exemption (8570-27)
- 1 copy Certification with Respect to Data (8570-34)
- 1 copy data matrix (confidential)
- 1 copy public data matrix
- 2 copies Confidential Statement of Formula
- 3 copies data transmittal document
- 3 copies Bayer Report No. 33714 (Domestic Animal Safety – Kittens)
- 3 copies Bayer Report No. 33741 (Child Resistant Packaging Study; 4-pack/child)
- 3 copies Bayer Report No. 33742 (Child Resistant Packaging Study; 4-pack/adult)
- 1 copy CD transmittal document
- 1 CD (electronic data file) for Bayer Report No. 33741
- 1 CD (electronic data file) for Bayer Report No. 33742

Transmittal Document

1. Name and Address of Submitter

Bayer HealthCare LLC
Animal Health Division
Box 390
Shawnee Mission, Kansas 66201-0390



Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs
(913) 268-2751

2. Regulatory Action in Which this Package is Submitted

Data submitted to support the proposed registration of Advantage® IGR 5 (EPA File Symbol 11556-XXX)

3. Transmittal Date

November 30, 2009

4. List of Submitted Studies:

<u>MRID No.</u>	<u>Volume</u>	
47924801	1	- "Evaluation of the General Safety of M881," 40 CFR Parts 160 and 792, T. J. Madsen, Report No. 33714, 193 p.
47924802	2	- "Child-Resistant Packaging (CRP) Child Panel Test of 4 x 0.23 mL Advantage® IGR KISI Blisters for Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, L. M. Dixon, Report No. 33741, 59 p.
47924803	3	- "Child-Resistant Packaging (CRP) Senior Adult Panel Test of 4 x 0.23 mL Advantage® IGR KISI Blisters for Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, L. M. Dixon, Report No. 33742, 251 p.

Appendix 1

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
ARIEL RIOS BUILDING - 1200 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 17, 2009



Dear Sir or Madam:

This letter is a final cancellation order, advising you that under Section 6(f)(1) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, EPA hereby cancels the registrations listed on the enclosure per your request for voluntary cancellation as listed in the Federal Register Notice dated March 18, 2009. The effective date of this cancellation order is the date of this letter.

As the basic registrant of the listed product(s) you may legally distribute or sell existing stocks of the canceled products until the disposition date listed on the enclosure. Existing stocks are defined as those stocks of a registered pesticide product which are currently in the United States and which have been packaged, labeled, and released for shipment prior to the effective date of the cancellation order.

It would be a violation of FIFRA for you or any supplementally registered distributor of your product(s) to distribute or sell any stocks currently in the United States which have been produced, packaged, labeled or released for shipment after the effective date of cancellation, or any existing stocks after the indicated disposition date. The Agency also expressly reserves the right to amend the existing stocks provisions of this Order if events should so warrant.

It is your responsibility as the basic registrant to notify any and all supplementally registered distributors of your product(s) that this cancellation order also applies to their supplementally registered products. You may be held liable for violations committed by your distributors.

Unless the provisions of an earlier order apply, existing stocks already in the hands of dealers or users can be distributed, sold or used legally until they are exhausted, provided that such sale and use comply with the EPA-approved label and labeling of the affected product(s).

Sincerely,

Kathryn Bowe for
Oscar Morales, Director
Information Technology and Resources Management Division

VOLUNTARY CANCELLATION ORDER (ENCLOSURE)

EPA CO NR: 11556

BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO BOX 390
SHAWNEE MISSION, KS 66201

Page 1

EPA PRODUCT REGISTRATION	DISP DATE	Product Name
11556-126	1/15/2010	Advantage Plus 9 for Cats
11556-129	1/15/2010	Advantage Plus 18 for Cats

Bayer HealthCare
Animal Health



Via Federal Express

July 24, 2008

Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle, PM Team 01
Registration Division

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Ms. Eagle:

Pursuant to Section 6(f) of *The Federal Insecticide, Fungicide, and Rodenticide Act* (FIFRA), Bayer HealthCare, Animal Health Division, is voluntarily cancelling the following registrations:

Advantage Plus 9 for Cats (EPA Reg. No. 11556-126)
Advantage Plus 18 for Cats (EPA Reg. No. 11556-129)

If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely,

Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs

DAS/lt



U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Ave., N.W.
Washington, D.C. 20460

EPA Reg. Number:

11556-126

Date of Issuance:

DEC 11 2007

NOTICE OF PESTICIDE:

☒ Registration
☐ Reregistration

(under FIFRA, as amended)

Term of Issuance:

From: December 11, 2007
To: December 11, 2008

Name of Pesticide Product:

Advantage Plus 9 for Cats

Name and Address of Registrant (include ZIP Code):

Bayer HealthCare LLC, Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is conditionally registered in accordance with FIFRA section 3(c)(7)(A) provided that you:

1. Within 1 year of the date of this letter, an acceptable Domestic Animal Safety study on kittens, using the approved formulation, must be received and approved by the Agency. This is a time-limited registration, therefore this registration will be allowed to expire on December 11, 2008 if an acceptable study is not submitted.
2. Submit and/or cite all data required for registration/reregistration/registration review of your product when the Agency requires all registrants of similar products to submit such data.
3. Make the following label changes before you release the product for shipment:
 - a. Revise the EPA Registration Number to read, "EPA Reg. No. 11556-126."
 - b. Revise the claim "Flea adulticide, larvicide, and ovicide" to read "Flea adulticide and ovicide."

Signature of Approving Official:

Date:

DEC 11 2007

Venus Eagle, Product Manager (01)
Insecticide-Rodenticide Branch, Registration Division (7505P)

- c. Revise the label claim "*Kills adult fleas, larvae, and eggs*" to read "*Kills adult fleas and eggs.*"
- d. The following claims are not appropriate for a cat label and must be deleted:
 - "*Remains effective after bathing and/or swimming*"
 - "*Remains effective following swimming and/or shampooing*"
- 4. The data requirements for storage stability (830-6317) and corrosion characteristics (830- 6320) have not been satisfied, and must be submitted within eighteen months of the date of this letter.
- 5. Submit one copy of the revised final printed label for the record before you release the product for shipment.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions.

A stamped copy of the label is enclosed for your records.

Venus Eagle
Product Manager (01)
Insecticide-Rodenticide Branch
Registration Division (7505P)

Enclosure

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

(Front Panel)

Advantage® Plus 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and
Kittens 9 Weeks and Older and 9 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

- Available only through licensed practicing veterinarians
- For use on cats and kittens 9 weeks of age and older
- Advantage Plus contains [imidacloprid], and [an/the] [insect growth regulator] [IGR] [pyriproxyfen] [Nylar®]*
- A single topical application remains effective for at least 4 weeks
- Convenient, easy to apply topical solution
- Once a month topical flea treatment for cats 9 weeks of age or older
- Advantage Plus is indicated for the prevention and treatment of fleas on cats 9 weeks of age and older
- For the treatment and prevention of flea infestations
- One treatment prevents further flea infestations for at least 4 weeks
- Kills 98-100% of the fleas on cats within 12 hours and continues to prevent infestations for at least four weeks
- Kills fleas before they lay eggs
- Larval flea stages in the cat's surroundings are killed following contact with an Advantage Plus treated cat
- Kills larval stages of fleas in the pet's environment
- Kills 98-100% of fleas within 12 hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Prevents flea eggs from hatching
- Effectively breaks the flea life cycle
- Effectively targets all [life] stages of [fleas]
- 3-way flea protection ([kills] [controls] adults, larvae, and eggs)
- Prevents flea eggs [and flea larvae] from developing into [(biting) (adult)] fleas
- Treatment with Advantage Plus rapidly kills fleas and may reduce the incidence of Flea Allergic Dermatitis [FAD]
- Flea adulticide, larvicide, and ovicide

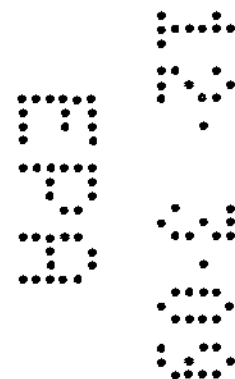
**ACCEPTED
with COMMENTS
In EPA Letter Dated:**

DEC 11 2007

**Under the Federal Insecticide,
Fungicide, and Rodenticide Act,
as amended, for the pesticide
registered under EPA Reg. No.
11556-126**

First
Page
Only

Appendix 2





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

JAN 12 2001

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

received
01/19/01

Subject: Applications for New Advantage Products
Reg. No. 11556-REA, REO, REL, REL, RET, RGN
Your submission date, April 7, 2000

Dear Mr. McNamara:

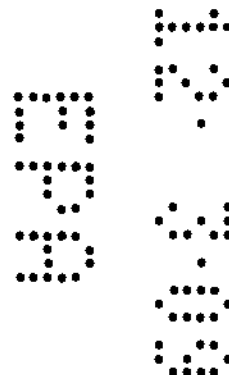
The labeling referred to above, submitted in connection with the above registrations under the Federal Insecticide, Fungicide, and Rodenticide Act have been reevaluated based on the additional information given, however, there are a number of things that the Agency insist upon and Bayer must comply but registration will be issued.

Enclosed are the conclusions issued by the Product Chemistry Branch. Please read the review and make changes as specified. Upon making the changes, please resubmit your labels and CSFs. If there are question, call me at 703 305-5409.

Sincerely,

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:



DATE: 22/NOV/2000

SUBJECT: **PRODUCT CHEMISTRY REVIEW OF MP [] EP's [X]**

DP BARCODE No.: D270181
REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats

AND

DP BARCODE No.: D270183
REG./File Symbol No.: 11556-REI
PRODUCT NAME: Advantage Plus 10 for Dogs

AND

DP BARCODE No.: D270184
REG./File Symbol No.: 11556-REL
PRODUCT NAME: Advantage Plus 20 for Dogs

AND

DP BARCODE No.: D270182
REG./File Symbol No.: 11556-REO
PRODUCT NAME: Advantage Plus 18 for Cats

AND

DP BARCODE No.: D270186
REG./File Symbol No.: 11556-RET
PRODUCT NAME: Advantage Plus 55 for Dogs

AND

DP BARCODE No.: D270188
REG./File Symbol No.: 11556-RGN
PRODUCT NAME: Advantage Plus 100 for Dogs

← FILE

COMPANY: Bayer Corporation

FROM: Linda L. Kutney, Chemist
Product Chemistry Team
Technical Review Branch (TRB)/RD (7505C) *Linda L. Kutney*
11-22-00

TO: Tina Levine/Dani Daniel, PM #4
Insecticide Branch/RD(7505C)

INTRODUCTION

The Bayer Corporation previously applied for registration of six new Advantage Plus insecticides
[REDACTED] intended to kill fleas on different sizes of
cats and dogs. The new products differs from the previous ones in that they include an insect
growth regulator, pyriproxyfen, to help control flea eggs, and contains an additional inert. 11/22/00

(L. Kutney) reviewed these data on June 2, 2000. All six products contain identical CSFs (dated 4-7-00) and separate proposed labels (dated 4-7-00). This review summarizes the Agency conclusions included in the June 2, 2000, review, Bayer's October 27, 2000, rebuttal to the Agency's conclusions and the Agency's response to Bayer's rebuttal.

Item 1

Agency Conclusion of June 2, 2000

Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the concentrations of the a.i.'s are correct and identical.

Bayer's Rebuttal of October 27, 2000

"The nominal concentrations of a.i.'s on the CSFs and the draft product labels are identical. For example, the upper and lower certified limits for imidacloprid are 9.6% and 8.6%, respectively, and the nominal concentration for imidacloprid is 9.1% on both the CSF and the draft labeling. Please note, the upper, lower and nominal concentrations for imidacloprid are identical to those on the CSFs and labels for the 7 registered Advantage products (EPA Reg. Nos. 11556-116 through 11556-122). For ease of reference, a CSF for Advantage 10, EPA Reg. No. 11556-117, is enclosed. The Confidential Appendix of the review states *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* As 8.9% is not on the CSF, we surmise that this value may have been calculated to correct for percent purity of the technical material. Thus, the nominal concentrations of the a.i.'s on the CSF are identical to the label concentrations, and the CSF and draft labeling for the Advantage Plus products are correct."

Agency Response of November 21

Subpart D-Product Chemistry Data Requirements, May 24, 2000, draft, defines the nominal concentration required by 158.155 as the "amount of active ingredient that is most likely to be present in the product when produced," in other words, the %active ingredient in the product (See also OPPTS 830.155, p.1). In addition, the nominal concentrations on the CSF and the draft label must be identical.

The Agency reiterates that *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* Bayer is correct in assuming that the nominal concentration of imidacloprid is corrected to account for the fact that technical imidacloprid a.i. [REDACTED] pure, and technical pyriproxyfen a.i. [REDACTED] pure.

The nominal concentration of each a.i. from the CSF is calculated, as follows:

nominal concentration of the a.i. =

The amount of each a.i. (kg), column 13a x (% purity of a.i. technical)
Total weight of components in column 13a

Bayer may either make sure that the label stated concentration is adjusted to be identical to the nominal concentrations of the a.i.'s or adjust the amount of each a.i. component so that the nominal concentration of each a.i. is identical to the proposed label concentration.

Item 2

Agency Conclusion of June 2, 2000

The name and address of the suppliers of inerts should be included on a revised CSF.

Bayer's Rebuttal of October 27, 2000

"Bayer acknowledges that the supplier(s) for "specialty" or proprietary materials must be listed on the CSF, but for those chemicals which are considered "commodity" chemicals, Bayer has not routinely listed the suppliers. As examples, the CSF's for the Advantage formulation (EPA Reg. Nos. 11556-116 through 11556-122) do not list the suppliers. The enclosed CSF for Advantage 10, EPA Reg. No. 11556-117, is a specific example. The Agency has permitted this in the past and acknowledges this practice which allows a change in source of these commodity chemicals without notification as permitted under PR Notice 98-10, Section III, B, 1.

As all of the inert ingredients in the proposed formulation for the A Plus products are commodity chemicals and are the same commodity chemicals which are in the Advantage formulation (Reg Nos 11556-116 through 11556-122) for which the Agency did not require the suppliers to be listed, Bayer would prefer not to list the suppliers of these chemicals for the Advantage Plus formulation."

Agency Response of November 21

The Agency routinely requests the names and addresses of suppliers of inerts on CSF's in order to be able to contact the supplier about the contents of their inerts, when necessary. The Instructions to EPA Form 8570-4, for Confidential Statement of Formula, Supplier Name and Address, number 11, specify that the Registrant should, "Provide the name and address of the supplier of each component in the (CSF) formulation. If one or more components will be obtained from more than one source, specify the names and addresses of the alternate sources also." There is no exception for "commodity chemicals."

A revised CSF including the name and address of the suppliers of inerts is still required.

Item 3

Agency Conclusion of June 2, 2000

The enforcement analytical method (40CFR 158.180) will be satisfactory, providing the Registrant submits a new copy not labeled "Confidential Business Information." This is a 3-97 FIFRA requirement (Section 10 (d)(1)) needed for enforcement purposes, etc.

Bayer's Rebuttal of October 27, 2000

"One copy of the method without any "confidential" markings is included with this letter. Please note that this method is to be used for all six product applications.

Agency Response of November 21

An analytical method labeled "CBI" is not permitted as an enforcement method. The Agency acknowledges the receipt of the enforcement analytical method without this label and considers that the requirement for analytical method (40CFR 158.180) is now satisfied.

Item 4

Agency Conclusion of June 2, 2000

Group B Product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 explodability (830-6315), Storage Stability of the Product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted.

Bayer's Rebuttal of October 27, 2000

Explodability "The OPPTS Test GDL 830.6316 for Explodability states 'The explodability test is necessary for use in precautionary labeling of pesticides when the product is potentially explosive.' Previous Agency guidance ('Roadmap for Guidance to Product Chemistry Guidelines' report from Anne Lindsay...) on this data requirement stated the requirement is for dusts and dusts from granular or powdered products. The Advantage Plus formulation is a liquid formulation. Moreover, it is not potentially explosive. The currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive..."

Agency Response of November 21

Explodability

The Agency is aware that Advantage Plus is a liquid formulation. Section 158.190 of the 40 Code of Federal Regulations states that explodability testing is required if the product is

potentially explosive. However, the requirement for data concerning explodability definitely applies to liquid end use products as well as dusts and dusts from granular or powdered products. In fact, some liquids have a very high explosive potential, e.g., nitroglycerine.

Registrants are obliged to characterize the explodability of new end use products, in the absence of data or documentation to the contrary, the Agency may consider that any new product may be potentially explosive. Bayer has now certified that the currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive...due to substitution of substitution of organic some organic solvent with water.

The requirement for explodability testing, OPPTS Test GDL 830.6316, is now satisfied.

Bayer's Rebuttal of October 27, 2000

Storage Stability As stated in 830.1000 Background for Product Properties Test Guidelines for the (viii) OPPTS 830.6317 Storage Stability discussion on p 17:

- "The requirement for data (storage stability) on the EP applies on when: The product use pattern is one for which performance (efficacy) data are required (40CFR 158.640); the results of the storage stability study indicate that the concentration of any active ingredient is not within the certified limits or degradates of toxicological significance are detected in the study; or product instability is suspected or incidents of instability are reported."

Advantage Plus does not meet any of these conditions, as it is an EP, it is not registered for the use patterns for which efficacy data are required under 40 CFR 158.640, and the product/a. i.'s are known to be stable. Thus, storage stability data for the Advantage Plus formulation should not be required for submission.

Agency Response of November 21

Product Properties Test Guidelines OPPTS 830.6317 (b) for Storage Stability states that, "The objective of storage stability testing is to determine how long the product will retain the percent a.i. in its packaging material corresponding to its useful shelf life. The storage stability study provides data on change (or lack of change) in product composition over time. If certain ingredients decompose, other new chemicals are formed whose toxicity and other characteristics must be considered." Bayer should read 830.6317 for details concerning the requirements for storage stability testing. Storage stability testing is required end-use formulations, including the Advantage Plus formulation.

Bayer's Rebuttal of October 27, 2000

Miscibility GDL 830.6319 for Miscibility states:

- "This test is intended to determine whether a pesticide solution is suitable for application

after dilution with oil or other nonpolar solvents where applicable, instead of water. Data on miscibility also provide necessary information to support acceptable labeling for tank mix and spray applications (if the tank mix of the pesticide product is oil based or diluted with oil)."

Agency Response of November 21

GDL OPPTS 830.6319 for miscibility states, "Data on the physical and chemical characteristics of pesticide products are used to confirm or provide supportive information on their identity. Such data are used in reviewing the production or formulation process to produce the pesticide or product." However, the Agency is willing to concede that, as stated in 40 CFR 158.190 "the miscibility test is required if the liquid is an emulsifiable liquid and is to be diluted with petroleum solvents." Provided there is no alteration of use pattern for Advantage Plus which would involve dilution with petroleum or non-polar solvents, there will be no requirement imposed for miscibility testing.

Bayer's Rebuttal of October 27, 2000

Dielectric Breakdown Voltage

...Advantage Plus is to applied directly to dogs and cats in small volumes...use is not around electric equipment...

Agency Response of November 21

GDL 830.6321 states that dielectric breakdown voltage is required when the pesticide product is used on or in the vicinity of electrical equipment and electrical conduits. Dielectric breakdown voltage will not be required for this product, provided there is no alteration of use pattern which would increase exposure of the pesticide handlers to electrical equipment or electrical conduits.

The requirement for data concerning dielectric breakdown voltage is now satisfied.

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP ☐ EP ☒
DP BARCODE No.: D265763 REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
COMPANY: Bayer Corporation

1. Reviewer: Linda L. Kutney
2. Company: Bayer Corporation
3. Type of Submission: Registration ☒ Reregistration ☐ New ☒ Resubmission ☐
Amendment ☐ "ME-TOO" ☒ Alternate Formulation ☐ Experimental Use Permit ☐
Other (Specify)
4. If "Me-TOO" Registration, this product is ☐ is not ☒ similar or substantially similar to
EPA's Reg. No.:
11556-116
If not, comment in Confidential Appendix on the significant differences between the registered
and the new source.

CONFIDENTIAL STATEMENT OF FORMULA

5. Type of formulation and the sources of active ingredients:
 - Non-integrated formulation system.....☒
 - Are all technical grade active ingredients used registered? • yes ☒ • no ☐. If no, specify
 - Integrated formulation system.....☐
6. Clearance of intentionally added ingredients in the formulation for the intended use
(indicate in the Confidential Appendix those that are not cleared; the PC Codes should be
provided by the chemist on the CSF for those that are cleared):
 - 6(a) Formulation intended for food use under 40CFR§180.1001:
 - yes ☐ • no ☒ • Some are cleared, others are not ☐
 - Cleared under list: • c ☐ • d ☐ • e ☐
 - Are there any limitations for use as an inert under 40CFR§180.1001?
 - yes ☐ • no ☒. If yes, specify
 - 6(b) Formulation intended for non-food use:
 - yes ☒ • no ☐ • Some are cleared, others are not ☐
 - 6(c) Clearance by the FDA of certain formulations under 21CFR§170 to 199, e.g., (a) indirect
food additives, such as food contact surface sanitizers; adhesives, coatings, paper and
paperboard products that may contact food in packaging or holding; & (b) substances

generally recognized as safe, GRAS

- yes [] • no [X] • Some are cleared, others not []

If yes, the entire formulation is cleared under 21CFR§

7. The density, pH, and flammability values given on the CSF are identical with those of GRN 830.7300(density), 830.7000(pH), and 830.6315(Flammability), respectively: •
yes [X] • no []
8. The nominal concentrations (NC) of the active ingredients and the upper and lower certified limits (UCL & LCL) are as follows:

Active ingredient(s)	REG-NO	% by weight		
		NC	UCL	LCL

Imidacloprid

Pyriproxyfen

9. The calculated NCs, based on the pure active ingredients (PAI), are identical to those on the label:

- yes [] • no [X]

Not acceptable for imidacloprid and Pyriproxyfen-as required in PR Notice 91-2

10. The certified limits are within the standard limits as per 40CFR§158.175 or are adequately explained if different: • yes [] • no [X]

PRODUCT LABEL

11. The chemical names of the active ingredients on the label are identical to those on the CSF: • yes [X] • no []

12. The appropriate physical and chemical hazards statement regarding flammability or explosive characteristics of the product are given on the label:

- yes [] • no [] • not applicable [X]

13. The storage and disposal instructions for the pesticide and container are in compliance with PR Notice 84-1 for household use products or PR Notice 83-3 for all other uses:

- yes [X] • no []

PRODUCT CHEMISTRY DATA (SERIES 830 Subgroup A & Subgroup B)

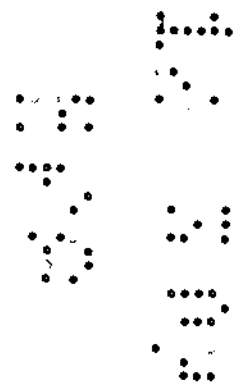
14. Chemical IDs/Manufacture/ Analytical Information New Guideline:830.--	Data Required Fulfilled	MRID No.
1550. Chemical Identity(CSF)	N	450969-02
1600. Beginning Materials 1620. Formulation Process	Y	450969-02
1670. Discussion of Impurities	Y	450969-02
1700. Preliminary Analysis	Y	450969-02
1750. Certified Limits(CSF)	N	450969-02
1800. Enforcement of Analytical Method	Y	450969-01

15. Physical/Chemical Properties New Guideline No. 830.---	Data Required Fulfilled	Value or Qualitat. Descrip.	MRID No.
6303. Physical State	Y	Liquid	450969-03
7300. Density/Bulk Density	Y	1.092 lbs/gal	450969-03
7000. pH	NA	6.02	450969-03
6314. Oxid/Red Action	Y	No ox. Or red. Action	450969-03
6315. Flammability-Flash Point	Y	above 100.2°C	450969-03
6315. Flame Extension	NA		--
6316. Explodability	Y	--	10-27-00 Bayer rebuttal
6317. Storage Stability.	N	--	--
7100. Viscosity	Y	5.13 cSt	450969-03

6319. Miscibility	Y	--	10-27-00 Bayer rebuttal
6320. Corrosion Characteristics	Y	Non-corrosive as packaged, tested for about 30 days	450969-03
6321. Dielectric Breakdown Voltage	Y	---	10-27-00 Bayer rebuttal

Explanations: Y = The Requirements Were Fulfilled; N = The Requirements Were Not Fulfilled;
NA = Not Applicable; G = Data Gap; U = Requires Upgrading; I = Incomplete or In Progress; W =
Waived.

Appendix 3



Doug
Spilker/SHAWN/AGCH
EM/US/BAYER

07/08/2009 11:18 AM

To Davis.Kable@epamail.epa.gov

cc

bcc Bruce Martin@BAYER-US-NOTES; Rex
Henry/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES;
Jochem
Rueter/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES;
john@ectodev.com

Subject Re: Advantage Plus (EPA Reg. Nos. 11556-125, -127, -128,
-130) - Final Stability Report

Bo,
We understand that the final 12-month storage stability study to support the registration of
the subject products is due to the Agency by May 31, 2010. As demonstrated by the
submission of the interim report, this study is in progress and we plan to meet the
Agency's deadline.

Sincerely,
Doug

Doug Spilker
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
ANIMAL HEALTH
Office: +1 913-268-2751
Mobile: +1 816-506-3102
Fax: +1 913-268-2135
Email: doug.spilker.b@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Powered by People, Driven by Science"

Davis.Kable@epamail.epa.gov



Davis.Kable
@epamail.ep
a.gov

07/07/2009
08:01 AM

To Doug Spilker <doug.spilker.b@bayer.com>

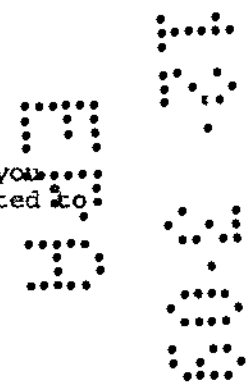
cc

Subject Re: Advantage Plus (EPA Reg. Nos. 11556-125, -127, -128,
-130) - Interim Stability Report

Doug-

Thanks for sending the interim report. Please confirm that you understand that the completed report must be formally submitted to the Agency by May 31, 2010.

Have a great Tuesday!
Bo



Kable Bo Davis, MS
Entomologist
U.S. Environmental Protection Agency
Insecticide-Rodenticide Branch
Registration Division (7505P)
1200 Pennsylvania Ave. NW
Washington, DC 20460

Tel: 703 306-0415
Fax: 703 305-6596
Email: davis.kable@epa.gov

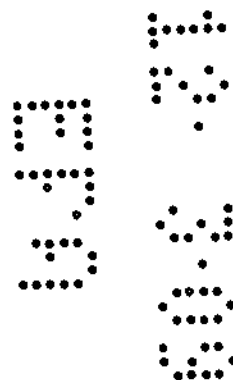
From: Doug Spilker <doug.spilker.b@bayer.com>
To: Kable Davis/DC/USEPA/US@EPA
Cc: Venus Eagle/DC/USEPA/US@EPA
Date: 07/02/2009 08:54 AM
Subject: Advantage Plus (EPA Reg. Nos. 11556-125, -127, -128, -130) - Interim Stability Report

Dear Mr. Davis,
Reference is made to the Agency's letter of April, 20, 2009, granting an extension in time to conduct the storage stability (830.6317) studies required to support the continued registration of the subject products.
As requested, please find attached our 3-month interim report for this study, showing that the product is within specifications at the 3-month testing point. The interim report also lists the other testing points for your information.

If you have any questions on this information, please let us know.

Sincerely,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
ANIMAL HEALTH
Office: +1 913-268-2751
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Email: doug.spilker.b@bayer.com



Address:

P.O. Box 390

Shawnee Mission, KS 66201-0390

Country: USA

Bayer Animal Health "Powered by People, Driven by Science"

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For alternate languages please go to

<http://bayerdisclaimer.bayerweb.com>

[attachment "Adv Plus Storage Stab Interim.PDF" deleted by Kable Davis/DC/USEPA/US]

Doug
Spilker/SHAWN/AGCH
EM/US/BAYER

07/02/2009 07:42 AM

To Kable Bo Davis,

cc Venus Eagle

bcc

Subject Advantage Plus (EPA reg. Nos. 11556-125, -127, -128, -130)

Dear Mr. Davis,

Reference is made to the Agency's letter of April, 20, 2009, granting an extension in time to conduct the storage stability (830.6317) studies required to support the continued registration of the subject products. As requested, please find attached our 3-month interim report for this study, showing that the product is within specifications at the 3-month testing point. The interim report also lists the other testing points for your information.

If you have any questions on this information,
please let us know.

Sincerely,
Doug

Douglas A. Spilker, Ph.D.
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Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Powered by People, Driven by Science"



Adv Plus Storage Stab Interim.PDF

Ecto Development Corporation
1229 N. Jesse James Road
Excelsior Springs, Mo 64024

Stability Report

Page 1 of 3

Product: Advantage Plus (Bayer HealthCare, LLC)(also known as M880 Insecticide)

Study No.: M880S02

Reg. No.: EPA Reg. No.: 11556-128, 11556-125, 11556-127,
11556-130*

Report To:	Joe Dyer	<u>Time Point</u>	<u>Date</u>	<u>Time Point</u>	<u>Date</u>
	Bob Pennington	0 month	03/25/09	12 month	03/25/10
	Cody Pennington	3 month	06/25/09	18 month	06/25/10
	Jochem Rueter	6 month	09/25/09	24 month	09/25 /10
		9 month	12/25/09		

Lot number, Size and Amount in Storage:

<u>Package</u>	<u>Lot</u>	<u>Size</u>	<u>Number in storage</u>
A	KP058CN	4 x 4 mL	40 packages
B	KP058CL	4 x 2.5 mL	40 packages
C	KP058CD	6 x 1 mL	40 packages
D	KP058CB	6 x 0.8 mL	40 packages
E	KP058CA	6 x 0.4 mL	40 packages

Packaging Type:

<u>Package</u>	<u>Bayer Tube</u>	<u>Bayer Foil No.</u>	<u>Bayer Lidding No.</u>
A			
B			
C			
D			
E			

Storage Location: Ecto stability Room B **Storage Conditions:** ambient room temperature

Stability type: GLP

Description: clear amber

*The four EPA registration numbers listed in this report are for the dog products. This stability study will also be used to support the proposed registration for cats. Package D, the 0.8 mL size, is for large cats and is not currently registered with EPA.

<u>Analyses</u>	<u>Target</u>	<u>Limits</u>	<u>Method</u>
Appearance		Conforms to description	visual (pass/fail)
Imidacloprid	9.10%	8.6%-9.6 % w/w	Ecto 105 (Bayer TMC 1402)
Pyriproxyfen	0.46%	0.41%-0.51% w/w	Ecto 105 (Bayer TMC 1402)
Corrosion of package	note any corrosion or changes in tube		visual (pass/fail)

Inert ingredient information may be entitled to confidential treatment

Stability Report

Page 2 of 3

Product: Advantage Plus (Bayer HealthCare, LLC)(also known as M880 Insecticide)**Study No.:** M880S02**Reg. No.:** EPA Reg. No.: 11556-128, 11556-125,
11556-127, 11556-130**% Imidacloprid (limits 8.6%-9.6% w/w)**

Time Point	Analyst/Date Reported	Package A	Package B	Package C	Package D	Package E
0 month	J. Rose -03/30/09	9.15	9.05	9.24	9.31	9.16
3 month	J. Rose -06/26/09	8.69	8.71	9.03	9.16	9.08
6 month						
9 month						
12 month						
18 month						
24 month						

% Pyriproxyfen (limits 0.41% - 0.51% w/w)

Time Point	Analyst/Date Reported	Package A	Package B	Package C	Package D	Package E
0 month	J. Rose -03/30/09	0.45	0.45	0.46	0.47	0.46
3 month	J. Rose -06/26/09	0.45	0.43	0.47	0.48	0.45
6 month						
9 month						
12 month						
18 month						
24 month						

Stability Report

Page 3 of 3

Product: Advantage Plus (Bayer HealthCare, LLC)(also known as M880 Insecticide)**Study No.:** M880S02**Reg. No.:** EPA Reg. No.: 11556-128, 11556-125,
11556-127, 11556-130**Product Appearance (clear amber)**

Time Point	Analyst/Date Reported	Package A	Package B	Package C	Package D	Package E
0 month	J. Rose -03/30/09	pass	pass	pass	pass	pass
3 month	J. Rose -06/26/09	pass	pass	pass	pass	pass
6 month						
9 month						
12 month						
18 month						
24 month						

Package appearance (no leaking, no corrosion, do tube deformation)

Time Point	Analyst/Date Reported	Package A	Package B	Package C	Package D	Package E
0 month	J. Rose -03/30/09	pass	pass	pass	pass	pass
3 month	J. Rose -06/26/09	pass	pass	pass	pass	pass
6 month						
9 month						
12 month						
18 month						
24 month						

Reported by: John E. Rose Date: 7/01/09



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Douglas A. Spilker
Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390



APR 20 2009

Dear Dr. Spilker:

Subject: Storage Stability and Corrosion Characteristics; Request for Time-Extension
EPA Registration No. 11556-125, 11556-127, 11556-128, 11556-130
Date Submitted: March 12, 2009

The Agency has received your request to extend the due date for submittal of storage stability (830.6317) and corrosion characteristics (830.6320) studies as required by Registration Notices dated September 18, 2007 for the products referenced above. These conditions of registration must be received by the Agency no later than May 31, 2010. If these conditions are not-complied with, the registrations will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions. If you have any questions regarding this letter, please contact me at (703) 306-0415.

Sincerely,

Kable Bo Davis
Entomologist
Insecticide-Rodenticide Branch
Registration Division (7505P)

Bayer HealthCare
Animal Health Division



Via Federal Express

March 12, 2009

Document Processing Desk (NO REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM01
Registration Division (7505P)

Subject: Advantage Plus 10 for Dogs (EPA Reg No. 11556-128)
Advantage Plus 20 for Dogs (EPA Reg No. 11556-125)
Advantage Plus 55 for Dogs (EPA Reg No. 11556-127)
Advantage Plus 100 for Dogs (EPA Reg No. 11556-130)
Requests for Extension in Time for Submission of
Storage Stability/Corrosion Studies:

Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201

Phone: 913 268-2000

Dear Ms. Eagle:

On September 18, 2007, the Environmental Protection Agency granted the Conditional Registration of the subject products, based on conditions among which was the submission of reports to fulfill the data requirements for storage stability (830-6317) and corrosion characteristics (830-6320). These data were to be submitted within eighteen months of the date of [the registration]. This letter is to request an appropriate extension in time for submission of these data to support the continued conditional registration of all four (4) products.

Although the registration of these products for use for flea control on dogs was granted, these products have never been produced, packaged or sold. As the Agency is aware, the original set of applications included two additional products with the identical formulation for use on cats and kittens. These registrations (11556-126 and -129) were subsequently voluntarily cancelled pursuant to Section 6(f) of FIFRA. Currently additional studies are in process to allow for Bayer Animal Health to apply for this same formulation to again be registered for use on cats and kittens.

It is Bayer's intention to wait to introduce these products as a full product line into the marketplace when all of the dog and cat products have been granted EPA registration. That is, we have no intention of producing, packaging or selling any of the products with this formulation until such time as we have submitted and received the new registration of the products for use on cats and kittens. All of these products (both dog and cat) contain the identical formulation, but packaged differently depending on the sizes of the animal.

As was discussed in the meeting March 5, 2009 with you and Mr. Davis, and subsequently agreed to in the e-mail of March 10, 2009 (Kable Davis to Doug Spilker), Bayer Animal Health will start the stability and corrosion studies to support the registrations of the subject products by April 1, 2009. We further agree to provide the Agency with a 3-month interim report from the stability studies. We therefore request a revised due date of May 31, 2010, for the completion and submission of the studies to fulfill the data requirements of storage stability (830-6317) and corrosion characteristic (830-6320).

If you need further information or clarification of this request, please call me (913-268-2751).

Sincerely,



Douglas A. Spilker, Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker.b@Bayer.com

DAS/lt

Appendix 4

95
38



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

August 30, 2000

MEMORANDUM

EPA File Symbol: 11556-REA Advantage® Plus 9 for Cats
DP Barcode: D265764
Case No: 068807
PC Codes: 129099 Imidacloprid; 129032 Pyriproxyfen

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505C)

Byron T. Backus
8/30/2000

To: Helene Daniel/Tina Levine, PM 04
Insecticide-Rodenticide Branch
Registration Division (7505C)

Registrant: Bayer Corp.

ACTION REQUESTED: Review a six-pack of acute toxicity studies. These studies are being used to support the proposed registrations of 6 products, which will be used to control fleas on domestic animals. The MRID numbers of these studies are 45096904 through 45096909.

COMMENTS AND RECOMMENDATIONS: The six acute toxicity studies have all been classified as acceptable, and the proposed product, EPA File Symbol 11556-REA

11556-REA

(ADVANTAGE PLUS 9 FOR CATS) has the following acute toxicity profile:

Acute Oral LD50	III	Acceptable
Acute Dermal LD50	IV	Acceptable
Acute Inhalation LC50	IV	Acceptable
Primary Eye Irritation	III	Acceptable
Primary Dermal Irritation	IV	Acceptable
Dermal Sensitization	No	Acceptable

These studies were conducted on a formulation containing 9.1% Imidacloprid and 0.9% Pyriproxyfen. The proposed product has a label declaration of 9.1% Imidacloprid and 0.46% Pyriproxyfen, with 90.44% inert ingredients.

It is emphasized that there are additional studies (companion animal safety studies) which have been submitted in support of the registration of this product. These companion animal safety studies should be reviewed and classified as acceptable before this product is registered.

Since the Oral LD₅₀ value is below 1500 mg/kg, and this product has residential uses, then it will require Child Resistant Packaging (CRP).

The following is the precautionary labeling for this product, based on the acute toxicity profile given above, and as obtained from the Label Review System:

Date: 08/30/00 LABEL REVIEW SYSTEM

ID #: 011556-00126 Advantage Plus 9 for Cats

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100, formerly §81-1))

Product Manager: 04
MRID No.: 45096904

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: September 30, 1999
Study No.: 99-A12-DZ

Testing Facility: Bayer Corporation, Agriculture Division Toxicology, Stilwell, Kansas
Author: Sturdivant, D.W.

Quality Assurance (40 CFR §160.12): Included (p. 6-7)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41

Species: Rat; Wistar Hannover (CrI:WI(Glx/BRL/Han)IGS BR
Age: Young adult (Males: 9-10 weeks; Females: approximately 12 weeks)
Weight: Males: 194-242 g; Females: 159-207 g
Source: Charles River Laboratories, Raleigh, NC

Conclusion:

1. LD₅₀ (mg/kg):
Males: = 1283 (95% C.L: 680-1678) mg/kg
Females: = 1000 (95% C.L: not calculable) mg/kg
Combined: = not reported
2. The estimated LD₅₀ is = 1000 mg/kg
3. Tox. Category: III Classification: Acceptable

Procedure (including deviations from 870.1100): "Groups of six male and six female rats were treated by gavage at varying concentrations of Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in vehicle (deionized water/PEG 200 1:1 v/v)." Groups of male rats were treated at nominal doses of 1000, 1500 and 2000 mg/kg while groups of female rats were treated at nominal doses of 500, 1000 and 2000 mg/kg... "Six male and six female rats were dosed with vehicle and served as concurrent control groups."

Results:

Dosage (mg/kg)*	Number of Deaths/Number Tested		
	Males	Females	Combined
0	0/6	0/6	0/12
500	-	0/6	-
1000	1/6	3/6	4/12
1500	5/6	-	-
2000	5/6	6/6	11/12

*Average actual doses were 0, 1038, 1542 and 2145 mg/kg for males and 0, 614, 1027 and 2071 mg/kg for females.

Observations: There were clinical signs of toxicity in the females dosed at 500 mg/kg. Symptoms at 1000 mg/kg included: brown nasal staining, brown oral staining, decreased activity, tremors and (females only) urine staining. Symptoms at 1500 and 2000 mg/kg included ataxia, decreased activity and tremors. Mortalities, when they occurred, were on days 0 to 2.

Gross Necropsy: "The following compound-related gross observations were observed at necropsy only in animals that were found dead: salivation and nasal discharge in males and females, red discolored lungs and urine in males. There were no gross observations noted in females from the 500 mg/kg dose group or in males from the 1000 mg/kg dose group. Also, there were no gross observations noted in any surviving, treated male or female rats or in control male or female rats.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200, formerly §81-2)

Product Manager: 04
MRID No.: 45096905

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: September 30, 1999
Study No.: 99-A22-EA

Testing Facility: Bayer Corporation, Agriculture Division Toxicology, Stilwell, Kansas
Author: Sturdivant, D.W. and Berry, L.A.

Quality Assurance (40 CFR §160.12): Included (p. 6-7)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41

Species: Rat; Wistar Hannover (CrI:WI(GIxBRL/Han)IGS BR
Age: Young adult (Males: approximately 9 weeks; Females: approximately 12 weeks)
Weight: Males: 192-245 g; Females: 174-210 g
Source: Charles River Laboratories, Raleigh, NC

Dermal LD₅₀ Testing:

Conclusion:

1. **LD₅₀ (mg/kg):**
 Males: > 5000 mg/kg (0/6 died)
 Females: > 5000 mg/kg (1/6 died)
 Combined: > 5000 mg/kg (1/12 died)
2. **The estimated LD₅₀ is** > 5000 mg/kg
3. **Tox. Category:** IV **Classification:** Acceptable

Procedure (Including deviations from 870.1200): "Hair from the dorsal and lateral areas of the trunk...was removed on the day prior to dose application... Groups of six males and six females each received a single dose of either 0 (deionized water) mg/kg or 5000 mg of the undiluted test substance/kg of body weight. For the animals treated with the Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On, measured aliquots of the undiluted test substance were applied uniformly... directly to the shaved area of the animal's back and then a plastic-backed, two-ply gauze patch... was used to cover the dosed area... The gauze patch was held in place with hypoallergenic tape. The animal was then wrapped with an elastic bandage, which was also secured with tape. After a minimum of 24 hours, the bandages and patch were removed and the dose site was wiped using paper towels dampened with tap water to remove as much test substance residue as feasible without inducing skin damage..."

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
0	0/6	0/6	0/12
5000	0/6	1/6	1/12

Observations: "One female from the 5000 mg/kg dose group...was found dead on post-

treatment day 2... Clinical signs of red lacrimal staining, nasal staining, fecal and urine staining in males and females are considered to be unrelated to treatment with the test substance since they occurred at a comparable incidence in control and treated animals. These signs as well as ungroomed appearance in two control males are ascribed to the manipulation and subsequent wrapping of the animal that is associated with dermal exposure and/or the use of Elizabethan collars... Compound-related clinical signs of decreased activity, labored breathing, and rales were observed in one treated female which died on post-treatment Day 2."

Gross Necropsy: "There were no compound-related gross observations noted at necropsy for the males or females that survived until terminal sacrifice. Observations of nasal discharge and urine stained ventrum were observed in one treated female that was found dead on post-treatment Day 2 and were considered compound-related."

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (8700.1300, formerly §81-3)

Product Manager: 04
MRID No.: 45096906

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: October 25, 1999
Study No.: 99-A42-EB

Testing Facility: Bayer Corporation, Agriculture Division Toxicology, Stilwell, Kansas
Author: Sturdivant, D.W.

Quality Assurance (40 CFR §160.12): Included (p. 6-7)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41

Species: Rat; Wistar Hannover (CrI:WI(GIxBRL/Han)IGS BR
Age: Young adult (Males: approximately 9 weeks; Females: approximately 12 weeks)
Weight: Males: 207-270 g; Females: 192-217 g

Source: Charles River Laboratories, Raleigh, NC

Conclusion:

1. **LC₅₀ (mg/L):**
 Males: > 2.50 mg/L (0/6 died)
 Females: > 2.50 mg/L (0/6 died)
 Combined: > 2.50 mg/L (0/12 died)
2. **The estimated LC₅₀ is** > 4.21 mg/L
3. **Tox. Category: IV** **Classification:** Acceptable

Procedure (including deviations from 8700.13): Exposure was for four hours, and was nose-only. "The test substance was generated as a liquid aerosol with a respirable particle size distribution."

Exposure Concentration ± S.D. mg/L (Analytically Determined)	Number of Deaths/Number Tested		
	Males	Females	Combined
0*	0/6	0/6	0/12
2.50 ± 1.10	0/6	0/6	0/12

*A group of 6 male and 6 female rats was "shamp-exposed to conditioned air via the nose-only route for a single four-hour period."

Clinical Observations: There were no deaths. "Clinical signs observed during this study were red perigenital staining, fecal staining and ungroomed appearance and were observed only on Day 0. Although the incidence of these signs was slightly higher in animals exposed to the test substance than air-control animals, they are considered a result of restraint during the exposure period and are not considered compound-related."

Gross Necropsy Findings: "No gross observations were observed at necropsy during this study."

Chamber Atmosphere			
Analytical Concentration	Nominal Concentration	MMAD (μm)	GSD
2.50 mg/L	3.20	2.61	3.02

59% of the particle mass was less than 4 μm , and 26% was less than 1 μm . These percentages are the means of 5 samples.

Other Information:

Chamber Environment *	
Chamber Volume	27 L
Airflow (exhaust flow rate)	28 LPM
Mean Chamber Temperature	23.5 °C
Relative Humidity	81%*

*The high relative humidity is attributed to a high percentage of water contained in the test substance formulation.

DATA REVIEW FOR PRIM~~ARY~~ EYE IRRITATION TESTING (870.2400, previously §81-4)

Product Manager: 04
MRID No.: 45096907
Sponsor Study No.: 99C-I35-FG

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: November 19, 1999
Study No.: Covance 90801932

Testing Facility: Covance Laboratories Inc., Madison, WI 53704
Author: Glaza, S.M.

Quality Assurance (40 CFR §160.12): Included (p. 4)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On; a clear, light-yellow liquid, Lot No. 99-901-73

Dosage: 0.1 mL

Species: Rabbits; Albino, Hra(NZW) SPF strain

Age: approximately 16 weeks of age

Weight: 2.57-2.707 kg

Source: Covance Research Products Inc., Kalamazoo, MI

Conclusion:

1. Toxicity Category: III
2. Classification: Acceptable

Procedure (including deviations from 870.2400): Three rabbits were used. "The test substance was administered as received... Initially one animal was treated and the results evaluated. Based on the irritation observed, the other two animals were then treated in the same manner. Each rabbit received 0.1 mL of the undiluted test substance placed into the everted lower lid of the right eye... The upper and lower lids were gently held together for 1 second to prevent loss of material and then released. The eyes of the rabbits remained unflushed immediately after treatment."

Observations	Number "positive"/number tested						
	Hours				Days		
	1	24	48	72	4	7	14
	Unwashed eyes						
Corneal Opacity	3/3	3/3	3/3	3/3	1/3	0/3	0/3
Iritis	3/3	3/3	3/3	2/3	1/3	0/3	0/3
Conjunctivae:							
Redness ¹	3/3	3/3	3/3	3/3	2/3	0/3	0/3
Chemosis ¹	3/3	3/3	3/3	2/3	0/3	0/3	0/3
Discharge ¹	3/3	2/3	3/3	2/3	0/3	0/3	0/3

¹Score of 2 or greater considered as a positive effect.

"Sodium fluorescein examinations were used to aid in revealing possible corneal injury at the observations conducted at 24, 48, 72, and 96 hours and Day 7 or until a negative response for

that animal was obtained."

Summary: "All 3 animals showed excessive pawing at the treated eye after test substance installation, and one animal vocalized following test substance instillation. All eyes had cleared by day 7 except for grade "1" conjunctival redness (not considered a positive response) in all 3 eyes; at day 14 all scores were zero.

DATA REVIEW FOR DERMAL IRRITATION TESTING (870.2500, previously §81-5)

Product Manager: 04
MRID No.: 45096908
Sponsor Study No.: 99C-I25-DL

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: October 6, 1999
Study No.: Covance 90503024

Testing Facility: Covance Laboratories Inc., Madison, WI 53704
Author: Glaza, S.M.

Quality Assurance (40 CFR §160.12): Included (p. 4)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On; a clear, light-yellow liquid, Lot No. 99-625-41

Dosage: 0.5 mL
Species: Rabbit; albino, HRA:(NZW)SPF
Age: approximately 15 weeks old
Weight: 2.308-2.554 g
Source: Covance Research Products Inc., Kalamazoo, MI

Conclusion:

1. **Toxicity Category:** IV
2. **Classification:** Acceptable

Procedure (including deviations from 870.2500): Three rabbits were used. "The undiluted test substance was applied to the intact skin site on each animal's back (approximate exposure area 6.25 cm²) in the amount of 0.5 mL. Each area of application was covered with an 8-ply 2.5-cm x 2.5-cm gauze patch secured with paper tape, loosely overwrapped with Saran Wrap®, and secured with Elastoplast® tape to provide a semioclusive dressing... At the end of the 4-hour exposure period, the patches were removed and the test sites were washed using liquid Ivory® soap mixed with water, rinsed with water, and dried with disposable paper towels. Any residual test substance was removed from the test sites as thoroughly as possible without irritating the skin."

Results: All scores (4, 24, 48 and 72 hrs) for erythema and edema were zero. The PII = 0.0

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600, formerly §81-6)

Product Manager: 04
MRID No.: 45096909
Sponsor Study No.: 99C-124-DN

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: October 6, 1999
Study No.: Covance 90503026

Testing Facility: FMC Corporation Toxicology Laboratory, Princeton, NJ 08543
Author: Freeman, C.

Quality Assurance (40 CFR §160.12): Included (p. 4)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On; a clear, light-yellow liquid, Lot No. 99-625-41

Positive Control Material: alpha-hexylcinnamaldehyde
Species: Guinea pigs, albino; Crl:(HA)BR
Age: Young adult; 5-7 weeks of age at initiation of dosing
Weight: 375-468 g
Source: Charles River Laboratories, Inc., Kingston, NY
Method: modified Buehler

Conclusion:

1. There is no indication that this product is a dermal sensitizer.
2. Classification: Acceptable

Procedure (Including deviations from 870.2600): A group of 20 guinea pigs (10M and 10F) were exposed to the test material during both induction and challenge, while an additional group of 10 (5M and 5F) served as the naive controls, and were exposed at challenge only. In the induction phase, "the undiluted test substance was applied to each animal in the test group by placing 0.4 mL on an adhesive patch (Hill Top Chamber®, 25-mm diameter) and placing the patch on the induction site along the dorsal anterior left quadrant. The patch was covered with dental dam and overwrapped with Elastoplast® tape. The dressing remained in place for a period of 6 hours after which it was removed. Any residual test substance was then removed from the application site using water and disposable paper towels.

The laboratory test system was validated by using alpha-hexylcinnamaldehyde as a positive control within the previous six months (positive control study completed August 4, 1999; study with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On was completed on October 6, 1999).

In the induction phase, 0.4 mL aliquots of the undiluted test material were applied using Hilltop Chambers, with 6-hour exposure periods. The animals in the test group received one application per week for a total of three applications. Challenge was 2 weeks after the last induction application with the same amount of test material at a previously unexposed site; in addition to the 20 animals which had been previously exposed, a group of 10 naive animals was similarly treated.

Results: There was no irritation (all scores were zero) at 24 hours following each induction application. At challenge, 2/20 previously induced animals, as well as 1/10 naive controls, showed a score of 0.5 at 24 hours. All animals (previously induced and naive control) scored 0 at 48 and 72 hrs following challenge treatment.

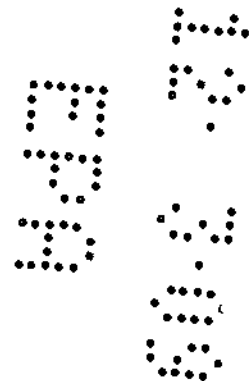
ACUTE TOX ONE-LINERS

1. DP BARCODE: D265764
2. PC CODE: 129099 Imidacloprid; 129032 Pyriproxyfen
3. CURRENT DATE: August 30, 2000
4. TEST MATERIAL: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41 (used for all studies except primary eye irritation); Lot No. 99-901-73 (used for primary eye irritation)

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/Bayer Corp. Toxicology/99-A12-DZ/SEP-30-1999	45096904	LD ₅₀ (M) = 1283 (95% C.L. 680-1678) mg/kg; LD ₅₀ (F) = 1000 (95% C.L. not calculable) mg/kg	III	A
Acute dermal toxicity/rat/Bayer Corp. Toxicology/99-A22-EA/SEP-30-1999	45096905	LD ₅₀ > 5000 mg/kg (0/6M, 1/6F females died following dosage at this level)	IV	A
Acute inhalation toxicity/rat/Bayer Corp. Toxicology /99A42-EB/OCT-25-1999	45096906	LC ₅₀ > 2.50 mg/L (males, females, combined). No mortalities following 4-hr exposure to this concentration.	IV	A
Primary eye irritation/rabbit/Covance Laboratories Inc./Covance 90801932/NOV-19-1999	45096907	Three eyes tested: All showed corneal opacity through 72 hrs. All eyes had cleared by day 7 except for grade "1" conjunctival redness (not considered a positive response) in all 3 eyes; at day 14 all scores were zero.	III	A
Primary dermal irritation/rabbit/ Covance Laboratories Inc./Covance 90503024/OCT-6-1999	45096908	All scores zero at 1, 24, 48 and 72 hrs. PII=0.00.	IV	A
Dermal sensitization/guinea pig/ Covance Laboratories Inc./Covance 90503026/OCT-6-1999	45096909	Not a sensitizer	-	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated

Appendix 5



Doug
Spilker/SHAWN/AGCHEM/US
/BAYER

03/31/2009 02:15 PM

To davis.kable@epa.gov

cc Harish
Chopade/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES

bcc Douglas
Hutchens/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES; Bruce
Martin/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES; Dan
Ciszewski/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES

Subject CRP Discussion with Dr. Gross

Bo,

Just a note. Rosalind Gross called today (~9:30 CDT), and Dr. Chopade (Bayer) and I spoke with her regarding her input on the document we recently (3/30/09) sent on the CRP testing. Since she called us, I assume you gave her the go-ahead. She had three basic comments to improve our testing:

1. We should use the most recent acute oral toxicity study (Bayer Report No. 75922; MRID 47089411) to calculate the Toxic Dose, rather than the one listed in the Reference - Page 1.
2. In the Tube Failure Criterion, it should be considered a failure if the child has access to any amount of water (from the tube).
3. In the Tube Failure Criterion (adults), it should be considered a failure if the participant opens the package improperly, that is not using scissors. How this should be discussed with Great Lakes Marketing (contractor).

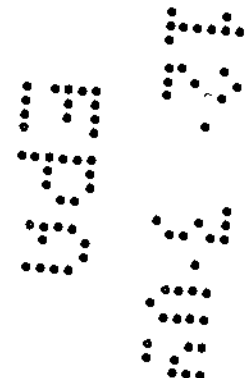
Since this was just guidance from her, it is our understanding that no additional action is needed by us, unless we have further questions.

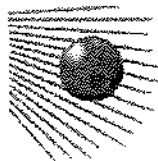
For your information,
Doug

Doug Spilker
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
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Bayer Animal Health "Powered by People, Driven by Science"





Davis.Kable@epamail.epa.gov
v

03/31/2009 04:52 AM

To Doug Spilker <doug.spilker.b@bayer.com>

cc

bcc

Subject Re: CRP Testing for Revised Packaging of Advantage Plus
Products

Excellent. Thanks, Doug. I will forward this information on.

Have a great, Tuesday.

Bo

Kable Bo Davis, MS
Entomologist
U.S. Environmental Protection Agency
Insecticide-Rodenticide Branch
Registration Division (7505P)
1200 Pennsylvania Ave. NW
Washington, DC 20460

Tel: 703 306-0415

Fax: 703 305-6596

Email: davis.kable@epa.gov

|----->
| From: |
|----->

>-----

| Doug Spilker <doug.spilker.b@bayer.com>
|

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| To: |
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>-----

| Kable Davis/DC/USEPA/US@EPA
|

>-----

|----->
| Cc: |
|----->

>-----

| Harish Chopade <harish.chopade.b@bayer.com>
|

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|----->
| Date: |
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| 03/30/2009 03:25 PM
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| Subject: |
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| CRP Testing for Revised Packaging of Advantage Plus Products
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Dear Mr. Davis,
Reference is made to the meeting of March 4, 2009 (BAH: D. Spilker;
EPA: B. Davis, V. Eagle and R. Gross), which included a discussion on
Advantage Plus for Dogs (11556-125, -127, -128, -130) and our plans to
develop revised packaging for these products, as well as for the
yet-to-be submitted Advantage IGR for Cats product. As you will recall,
these products require child-resistant packaging. As we discussed, we
understand that the full battery of tests with children and adult
seniors, as well as with all package sizes (colors) and all package
configurations (4-packs and 6-packs) is required. We will conduct these
tests as before with Great Lakes Marketing Company, Toledo, Ohio.

In the aforementioned meeting, we discussed with Dr. Rosalind Gross the
CRP Testing plans. In that conversation, Dr. Gross requested we send her
some specific information about our protocol: a) the test failure
criteria and b) confirmation that we will specifically instruct seniors
to use only the scissors provided during the tests. To that end,
please find attached a summary document addressing Dr. Gross' questions,
including information especially on the toxic dose calculations, total
number of studies needed, and the test failure criteria proposed for the
CRP testing of Advantage Plus/IGR blisters. The failure rates shown in
the attached are the same as used in the previously conducted studies (
Child test example: Bayer Report No. 75897; MRID 47089103 and Adult test
example: Bayer Report No. 75898; MRID 47089104) that were used to
support the currently registered Advantage Plus product/packages.

We request that this information be forwarded to Dr. Gross to answer her
questions. We are planning to conduct these studies in mid-April, so if
Dr. Gross has any questions or comments, we would appreciate her
feedback as soon as it is available.

Sincerely,

Doug Spilker

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
ANIMAL HEALTH
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Mobile: +1 816-506-3102
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Country: USA

Bayer Animal Health "Powered by People, Driven by Science"

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For alternate languages please go to <http://bayerdisclaimer.bayerweb.com>
[attachment "Advantage IGR CRP Testing -For EPA Review 3-27-09.doc"
deleted by Kable Davis/DC/USEPA/US]

Doug
Spilker/SHAWN/AGCHEM/US
/BAYER

03/30/2009 02:21 PM

To davis.kable@epa.gov
cc Harish
Chopade/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES
bcc Mary
Hunt/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES;
Dan
Ciszewski/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES;
Bruce
Martin/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES;
Douglas
Hutchens/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES;
Jagdeep
Buch/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES
Subject CRP Testing for Revised Packaging of Advantage Plus
Products

Dear Mr. Davis,

Reference is made to the meeting of March 4, 2009 (BAH: D. Spilker; EPA: B. Davis, V. Eagle and R. Gross), which included a discussion on Advantage Plus for Dogs (11556-125, -127, -128, -130) and our plans to develop revised packaging for these products, as well as for the yet-to-be submitted Advantage IGR for Cats product. As you will recall, these products require child-resistant packaging. As we discussed, we understand that the full battery of tests with children and adult seniors, as well as with all package sizes (colors) and all package configurations (4-packs and 6-packs) is required. We will conduct these tests as before with Great Lakes Marketing Company, Toledo, Ohio.

In the aforementioned meeting, we discussed with Dr. Rosalind Gross the CRP Testing plans. In that conversation, Dr. Gross requested we send her some specific information about our protocol: a) the test failure criteria and b) confirmation that we will specifically instruct seniors to use only the scissors provided during the tests. To that end, please find attached a summary document addressing Dr. Gross' questions, including information especially on the toxic dose calculations, total number of studies needed, and the test failure criteria proposed for the CRP testing of Advantage Plus/IGR bilsters. The failure rates shown in the attached are the same as used in the previously conducted studies (Child test example: Bayer Report No. 75897; MRID 47089103 and Adult test example: Bayer Report No. 75898; MRID 47089104) that were used to support the currently registered Advantage Plus product/packages.

We request that this information be forwarded to Dr. Gross to answer her questions. We are planning to conduct these studies in mid-April, so if Dr. Gross has any questions or comments, we would appreciate her feedback as soon as it is available.

Sincerely,
Doug Spilker

Douglas A. Spilker, Ph.D.
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Country: USA

Bayer Animal Health "Powered by People, Driven by Science"



Advantage IGR CRP Testing -For EPA Review 3-27-09.doc

Child-Resistant Packaging and Toxicology of Advantage® IGR Formulation for Use in Cats and Dogs for Flea Control

INTRODUCTION

The packaging requirements for pesticides and devices to be marketed in the United States are prescribed in Code of Federal Regulations, 40 CFR Part 157.20. Bayer Animal Health has developed a new product, Advantage® IGR (previously known as Advantage® Plus), containing 9.1% imidacloprid and 0.46% pyriproxyfen as a spot-on formulation for dogs and cats for the control of fleas (all stages). The product will be marketed as three different sized tubes (1.0-mL, 2.5-mL and 4.0-mL total capacity) packaged in a 4-pack and 6-pack child resistant blisters. For cats, 0.23 mL, 0.4 mL or 0.8 mL product will be placed in a 1.0-mL capacity tube. For dogs, 0.4 mL or 1.0 mL product will be placed in a 1.0-mL tube, 2.5 mL product in a 2.5-mL tube, and 4.0 mL product in a 4.0-mL tube. The child-resistant (CR) feature of the packaging is the blisters. The tubes are not child-resistant; tubes will be identical to those currently marketed for Advantage® and K9 Advantix® products.

CALCULATION OF TOXIC DOSE

The acute oral LD₅₀ for this new product (formulation with 9.1% imidacloprid and 0.9% pyriproxyfen) was determined to be 1,283 mg/kg for male and 1,000 mg/kg for female rats.¹ This product meets the US EPA 40 CFR Part 157.22 requirements for child-resistant packaging according to the following toxicity criteria: (1) Toxicity criterion – the pesticide has an oral LD₅₀ of 1.5 g/kg or less, and (2) Use criterion – The product's labeling either directly recommends residential use or reasonably can be interpreted to permit residential use.

In Table 1, below, are given the number of tubes of each different size of this product a child weighing 25 pounds (11.4 kg) would have to ingest to reach a toxic dose (amount). "Toxic dose" for this product as defined in 40 CFR Part 157.22 and that confirmed by Dr. Rosalind Gross of US EPA is the acute oral LD₅₀ value. Thus, to err on the conservative side, the LD₅₀ value of 1,000 mg/kg (= 1.0 g/kg) for female rats was used in the supporting calculations. The density of the product, 1.092 g/mL, was also used in the supporting calculations. A toxic dose of the Advantage® IGR formulation for a child (25 lb = 11.4 kg) is calculated as 10.44 mL of Advantage® IGR product [i.e., (1.0 g/kg LD₅₀ x 11.4 kg body weight) ÷ (1.092 g/mL density) = 10.44 mL].

Table 1. Tube Sizes, Number of Tubes as Toxic Dose for a Child, and Test Failure Criteria

Advantage® IGR Tube Size (mL)	No. of Tubes* Constitute as Toxic Dose for a Child	Test Failure Criteria (# Tubes Accessed by a Child)
0.23	46 (45.4)	9**
0.4	27 (26.1)	9
0.8	13 (13.05)	9
1.0	11 (10.4)	9
2.5	5 (4.2)	5
4.0	3 (2.6)	3

*Calculated tube number in the parenthesis (with ≥ 0.1 fraction) is rounded off to the next higher integer. All tubes are single use, which means each tube contents are used as a single application.

**Per EPA guidance, 9 tubes is recommended as the test failure criteria for child panel testing when ≥ 9 tubes represent a toxic dose for a child.

Reference: 1. Sturdivant, D.W. 1999. Acute oral LD₅₀ toxicity study with imidacloprid (9.1%)/pyriproxyfen (0.9%) spot-on in rats, Bayer Animal Health Report No. 75195, MRID No. 45096904.

CRP TESTING OF BLISTERS

Bayer is planning on testing Advantage® IGR blisters made with two different lidding foils: Tropical foil and PVC foil. As individual tube sizes of Advantage® IGR to be marketed for dog and cat will be colored differently, we are going to CRP test individual tube size and blister type (4-pack or 6-pack). Therefore, for blisters with either Tropical or PVC lidding foil, there will be a total of 8 CRP studies (8 child panel + 8 senior adult panel) for the dog product (Table 2) and 5 CRP studies (5 child panel + 5 senior adult panel) for the cat product (Table 3) for each lidding foil type blisters. As a guideline requirement for CRP testing purposes, all tubes will be filled with appropriate volume of water.

Table 2. Blister Packaging (CRP Studies) for Dogs

Tube Size* & Color Scheme	Blister Type	No. of Tubes = Toxic Dose to a 25-lb Child	Test Failure Criteria to be Followed (Minimum # of Tubes Accessed by a Child)
0.4 mL Green (Pantone 346C)	4 pack	27	9
	6 pack	27	9
1.0 mL Turquoise (Pantone 311C)	4 pack	11	9
	6 pack	11	9
2.5 mL Red (Pantone 197C)	4 pack	5	5
	6 pack	5	5
4.0 mL Blue (Pantone 543C)	4 pack	3	3
	6 pack	3	3

*Each tube will contain appropriate volume of water.

Table 3. Blister Packaging (CRP Studies) for Cats

Tube Size* & Color Scheme	Blister Type	No. of Tubes = Toxic Dose to a 25-lb Child	Test Failure Criteria to be Followed (Minimum # of Tubes Accessed by a Child)
0.23 mL Turquoise (Pantone 326C)	4 pack	46	9
0.4 mL Orange (Pantone 157C)	4 pack	27	9
	6 pack	27	9
0.8 mL Purple (Pantone 264C)	4 pack	13	9
	6 pack	13	9

*Each tube will contain appropriate volume of water.

CONDUCT OF CRP STUDIES

Both child panel and senior adult panel CRP studies for each blister & tube size (water-filled) will be performed according to the test protocol prescribed in the Federal Register, Title 16, Part 1700.20, by Great Lakes Marketing, Toledo, Ohio. Data collected for the studies will be analyzed and reported according to the Agency guidelines. Also, CRP protocol test data will be made available to the Agency electronically on a CD-R.

A Tube Failure Criterion in Child Panel Testing: In child panel testing (50 to 200 participants), any small breach of a blister cavity (clearly visible small incision or opening) made by a child with finger nails or teeth would be counted as one tube failure.

Use of a Pair of Scissors in Senior Adult Panel Testing: A senior adult panel will include 100 participants. As the blister Opening Instructions involve the use of a pair of scissors, senior adult participants will be allowed to use a pair of scissors during the testing, but they will be warned against using a pocket knife or other tools.

Appendix 6

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EFFICACY REVIEW

PRODUCT: Advantage Plus 10 for Dogs, Advantage Plus 20 for Dogs, Advantage Plus 55 for Dogs, Advantage Plus 100 for Dogs

FILE SYMBOL: 11556-REI, 11556-REL, 11556-RET, 11556-RGN

DATE: August 6, 2007

DP BARCODE: D342416, D342417, D342418, D342419

DECISION NUMBER: 215323, 215314, 215321, 215493

GLP: No

CHEMICAL: Imidacloprid (9.1%)

CHEMICAL NUMBER: 129099

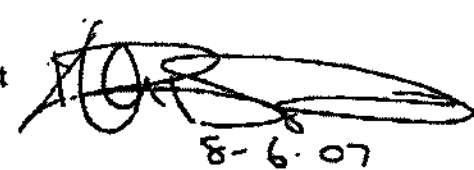
PURPOSE: Review data to support the addition of dog lice (*Trichodectes canis*)

MRID: 47190401. Doyle, J., Egan, T. (2006) A Controlled Randomised Study to Evaluate the Efficacy of Advantage Against a Natural Infestation of Dog Lice (*Trichodectes canis*) Following a Single Topical Administration to Adult Mixed Breed Dogs: Final Study Report. Project Number: 144/914, 75950. Unpublished study prepared by Charles River Laboratories BioLabs Europe. 130p.

TEAM REVIEWER: Kahle Bo Davis

EFFICACY REVIEWER: Kahle Bo Davis, M.S., Entomologist

SECONDARY EFFICACY REVIEWER: Joanne Edwards, M.S., Entomologist



8-6-07

BACKGROUND:

Advantage Plus 10, Advantage 20, Advantage 55 and Advantage 100 are ready to-use spot on treatments for dogs intended for the month long control of fleas and lice. The proposed labels contained the following label claims concerning lice:

1. Once-A-Month Topical Treatment for Fleas and Lice
2. Kills [(biting) (chewing)] lice
3. Kills [(biting) (chewing)] lice, which may serve as intermediate hosts for tapeworms (*Dipylidium caninum*)
4. Kills [(biting) (chewing)] lice and prevents further infestations

DATA REVIEW:

The following data review is comprised of explanations of materials and methods, and a summation of experimental results containing tables with reformatted data.

47190401. Doyle, J., Egan, T. (2006) A Controlled Randomised Study to Evaluate the Efficacy of Advantage Against a Natural Infestation of Dog Lice (*Trichodectes canis*) Following a Single Topical Administration to Adult Mixed Breed Dogs: Final Study Report. Project Number: 144/914, 75950. Unpublished study prepared by Charles River Laboratories BioLabs Europe. 130p.

The experimental design consisted of separating 20 dogs into two groups of ten containing both males and females. All dogs included in the study were naturally infested with dog lice (*Trichodectes canis*) and had a minimum of 10 infesting lice. Group 1 acted as a control, while dogs within the second group were treated (via spot treatment) with 0.1 mL/kg bodyweight of Advantage on day 0. Observations on efficacy were taken on days 1, 2, 7, 14, 21, 28 and 36.

Results:**Table 1. Lice Counts**

Group	Animal	Total Number of Lice								
		Day 1	Day 2	Day 7	Day 14	Day 21	Day 28	Day 36		
Control	1	-	52	-	86	92	52	52	95	68
	2	-	-	77	-	66	63	72	-	90
	3	21	29	54	9	3	0	0	0	0
	4	20	80	13	15	1	0	0	0	0
	5	85	44	61	88	64	49	81	85	44
	6	79	36	53	-	80	76	57	83	89
	7	-	70	61	88	66	59	97	99	81
	8	31	37	32	46	37	16	13	25	42
	9	-	-	-	-	99	94	91	75	
	10	-	72	-	-	95	65	65	69	49
Treatment	1	36	29	3	0	0	0	0	0	0
	2	-	67	1	0	0	0	0	0	0
	3	-	74	4	5	0	2	0	0	0
	4	-	96	16	10	0	0	0	0	0
	5	-	91	20	6	0	0	0	0	0
	6	-	-	68	13	0	0	0	0	0
	7	59	47	0	0	0	0	0	0	0
	8	-	42	22	0	0	0	0	0	0
	9	73	41	1	0	0	0	0	0	0
	10	41	35	4	0	0	0	0	0	0

Table 2. Efficacy Results

Day	% Efficacy (mean)
1	91%
2	98%
7	100%
14	100%
21	100%
28	100%
36	100%

The percent efficacy ranged from 91% (1 day) to 100% (days 7 – 36).

RECOMMENDATIONS:

The submitted data support the addition of biting or chewing lice to products: 11556-REI, 11556-REL, 11556-RET and 11556-RGN. The following recommendation applies:

1. Revise the label claim "*Kills [(biting) (chewing) lice, which may serve as intermediate hosts for tapeworms (Dipylidium caninum)*" to read "*Kills fleas, which may serve as intermediate hosts for tapeworms*".

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Appendix 7

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

22/SEP/2000

MEMORANDUM

Subject: EPA File Symbol: 11556-REA Advantage Plus 9 for Cat,
11556-REO Advantage Plus 18 for Cats
DP Barcodes: D265762 and D265765
Case No: 068807, 068810
PC Code: 129099

From: Masih Hashim, Toxicologist *MH*
Technical Review Branch *SCR*
Registration Division (7505C)
To: Helene Daniel/Tina Levine, PM 04
Insecticide Rodenticide Branch
Registration Division (7505C)

Registrant: Bayer Corporation

ACTION REQUESTED: The Registrant requests a review of the companion animal safety study (MRID 45097001), Advantage Plus® 9 and 18 for cats with: 9.1% Imidacloprid w/w; 0.9% Pyriproxyfen w/w (active ingredients). The compound was topically applied at 5 times (limit test) the recommended dose to groups of 6 male and 6 female cats. Animals were treated on study days 0, 7, 14, and 21.

COMMENTS/RECOMMENDATIONS:

The study MRID 45097001 was conducted at 5X the specified application rate; which demonstrates an adequate safety margin for adult cats. There was no repeated toxicological response in cats following exposure to the proposed formulation. Any such response is random and is seen in the earlier phase of study. This cat study has been classified as **Acceptable**.

The Products: 11556-REA and/or 11556-REO have Imidacloprid 9.15% and Pyriproxyfen 0.9%. However, the label states 9.1% Imidacloprid and 0.46% pyriproxyfen, having same formulation for both products.

This product has residential uses and an Oral LD₅₀ value < 1500 mg/kg, which would require the Child Resistant Packaging.

Acute toxicology profile for the Product is as follows:

Acute Oral LD ₅₀	III	acceptable
Acute Dermal LD ₅₀	IV	acceptable
Acute Inhalation LC ₅₀	IV	acceptable
Primary Eye Irritation	III	acceptable
Primary Dermal Irritation	IV	acceptable
Dermal Sensitization	neg	acceptable

Primary review of the Companion Animal Safety Study was conducted by an Agency Contractor, then revised by the Technical Review Branch. There are two labels, one for Advantage Plus 9 for Cats and the other for Advantage Plus 18 for Cats.

Following is the Executive Summary of the study:

In a companion animal safety study (MRID 45097001), Advantage Plus® 9 and 18 for cats (Active Ingredients: 9.1% Imidacloprid w/w; 0.9% Pyriproxyfen w/w) was topically applied at dose volumes of 2.0 ml for cats weighing less than or equal to 9 lbs, and 4.0 mL for cats weighing greater than 9 lbs (5 times the recommended doses) to groups of 6 male and 6 female cats, 7 months to one year of age. Controls were dosed with the vehicle at volumes of 2.0 mL for cats weighing less than or equal to 9 lbs and 4.0 ml for cats weighing greater than 9 lbs (5.6 times the volume of vehicle in the recommended doses). Animals were treated on (study) days 0, 7, 14, and 21.

Treatment related clinical signs included transient salivation which ceased within 2 hours of treatment on day 0 (4 of 12 test animals and 1 of 12 vehicle control animals reported from licking the test material), and a rough hair coat appearance at the treatment site on all animals of both groups following treatment on days 14 and 21. None of the cats were observed salivating following the last 3 treatments. One animal from the test group had pruritis at one hour on day 21. There was vomiting by two cats in the test group on days 19 and 25, which did not occur in periods following the test (substance) applications. Vomiting may be associated with licking the test substance. This does not appear to be exposure related. There were loose stools from two cats in the control group. Additionally, one male from the control group exhibited inappetence on days 22-24 and was observed to be circling and unsteady at the p.m. observation period on day 23. The clinical chemistry and hematology findings from this cat on day 22 were consistent with hemoconcentration due to dehydration. Possible cause of these signs was not clear. His behavior and appetite were normal for the remainder of the study, as were his clinical pathology parameters. There were no other treatment related effects on hematology, coagulation or clinical chemistry parameters. There were no treatment related effects on body weight or food consumption, and there were no signs of irritation at the application sites.

Currently there is a product in the market with 9.1% Imidacloprid. The proposed product is adding 0.46% Pyriproxyfen to the current product. The added ingredient has low acute and chronic toxicity in mammalian species.

Any clinical signs on the study showed no consistent toxicological response. This study is classified as Acceptable /Guideline for a companion animal safety study (OPPTS 870.7200) in cats.

LABELING:

Date: 09/28/00 LABEL REVIEW SYSTEM

ID #: 011556-00126 Advantage Plus 9 for Cats

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow.

Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

USER SAFETY RECOMMENDATION

Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

Date: 09/28/00

LABEL REVIEW SYSTEM

ID #: 011556-00129 Advantage Plus 18 for Cats

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow.

Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

USER SAFETY RECOMMENDATIONS: Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

DATA EVALUATION REPORT

ADVANTAGE PLUS® 9 AND 18 FOR CATS
[9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation]

STUDY TYPE: Companion Animal Safety - Cat (OPPTS 870.7200)
MRID 45097001

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:

Donna L. Fefee, D.V.M.

Signature:

Date:

Robert H. Ross
for D.L. Fefee
AUG 14 2000

Secondary Reviewers:

Cheryl B. Bast, Ph.D., D.A.B.T.

Signature:

Date:

Cheryl B. Bast
AUG 14 2000

Robert H. Ross, M.S., Group Leader

Signature:

Date:

Robert H. Ross
AUG 14 2000

Quality Assurance:

Lee Ann Wilson, M.A.

Signature:

Date:

L. A. Wilson
AUG 14 2000

Disclaimer

This review may have been altered subsequent to the contractors signatures above.

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Cats[OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODES: D265762, D265765; MRID NUMBER: 45097001

TEST MATERIAL: Advantage Plus® 9 and 18 for Cats

STUDY NUMBER: 75122 (150.853)

TESTING FACILITY: Bayer Corporation, Agriculture Division, Animal Health, DeSoto Research Facility, 35040 West 87th Street, Building Number 20, DeSoto, Kansas 66018.

SPONSOR: Bayer Corporation, Agriculture Division, Animal Health

TITLE OF REPORT: Evaluation of the general safety of 9.1% Imidacloprid with 0.9% pyriproxyfen spot-on formulation in the target species, adult cats.

AUTHOR: A.S. Abraham

REPORT ISSUED: April 4, 2000

EXECUTIVE SUMMARY:

In a companion animal safety study (MRID 45097001), Advantage Plus® 9 and 18 for cats (Active Ingredients: 9.1% Imidacloprid w/w; 0.9% Pyriproxyfen w/w) was topically applied at dose volumes of 2.0 ml for cats weighing less than or equal to 9 lbs, and 4.0 mL for cats weighing greater than 9 lbs (5 times the recommended doses) to groups of 6 male and 6 female cats, 7 months to one year of age. Controls were dosed with the vehicle at volumes of 2.0 mL for cats weighing less than or equal to 9 lbs and 4.0 ml for cats weighing greater than 9 lbs (5.6 times the volume of vehicle in the recommended doses). Animals were treated on (study) days 0, 7, 14, and 21.

Treatment related clinical signs included transient salivation which ceased within 2 hours of treatment on day 0 (4 of 12 test animals and 1 of 12 vehicle control animals reported from licking the test material), and a rough hair coat appearance at the treatment site on all animals of both groups following treatment on days 14 and 21. None of the cats were observed salivating following the last 3 treatments. One animal from the test group had pruritis at one hour on day 21. There was vomiting by two cats in the test group on days 19 and 25, which did not occur in periods following the test (substance) applications. Vomiting may be associated with licking the test substance. This does not appear to be exposure related. There were loose stools from two cats in the control group. Additionally, one male from the control group exhibited inappetence on days 22-24 and was observed to be circling and unsteady at the p.m. observation period on day 23. The clinical chemistry and hematology findings from this cat on day 22 were consistent with hemoconcentration due to dehydration. Possible cause of these signs was not

clear. His behavior and appetite were normal for the remainder of the study, as were his clinical pathology parameters. There were no other treatment related effects on hematology, coagulation or clinical chemistry parameters. There were no treatment related effects on body weight or food consumption, and there were no signs of irritation at the application sites.

Currently there is a product in the market with 9.1% Imidacloprid. The proposed product is adding 0.46% Pyriproxyfen to the current product. The added ingredient has low acute and chronic toxicity in mammalian species.

Any clinical signs on the study showed no consistent toxicological response. This study is classified as **Acceptable /Guideline** for a companion animal safety study (OPPTS 870.7200) in cats .

I. MATERIALS

A. Test material

9.1% Imidacloprid with 0.9% Pyriproxyfen (w/w) Spot-on Formulation (Advantage Plus® 9, and 18 for Cats)

Description: not provided

Lot No.: 99-901-66

Active Ingredients: Imidacloprid, 9.1% (w/w); Pyriproxyfen, 0.9% (w/w)

Storage Conditions: in the dark in a closed cabinet at room temperature

B. Administration: Topical (spot-on)

C. Vehicle and/or positive control

The control animals received the vehicle.

D. Test animals

Species: Cat

Breed: Domestic shorthair

Age and weight at study initiation: 7-12 months; males: 3.8-5.1 kg., females: 2.4-3.1 kg

Source: Liberty Research Inc., 170 Route 17C, P.O. Box 107, Waverly, New York

Housing: Individually in cages with approximately 7.5 square feet of floor space

Diet: Commercial feed purchased from Harlan Teklad, Madison, Wisconsin, once daily

Water: Tap water, *ad libitum*

Environmental conditions:

Temperature: not reported

Humidity: not reported

Air changes: not reported

Photoperiod: not reported

Acclimation period: 14 days

H. STUDY DESIGN

A. In life dates: start: August 11, 1999; end: September 21, 1999

B. Animal assignment/ Dosage and Administration

Cats were assigned to the groups in Table 1 using stratified blocked randomization according to weight. Group 1 received the test substance at 5X the label specified use volume, and group 2 received the vehicle without the two active ingredients at a volume equivalent to the 5X use rate volume of the test substance. The dose volume was 2.0 mL for cats of either group weighing less than or equal to 4.1 kg (9 lbs) and 4.0 mL for cats of either group weighing greater than 4.1 kg. Treatments were applied on the back, from the back of the head to the shoulder. Animals were dosed on Study Days 0, 7, 14, and 21. Dose volumes for treatments on study days 0 and 7 were determined using body weights from study day -1, and dose volumes for treatments on study days 14 and 21 were determined using body weights from study day 13.

TABLE 1. Study design					
Group	Number of animals		Dose volume (mL)/multiple of recommended dose		Number of applications ^a
	Male	Female	Body weight ≤ 9 lbs	Body weight > 9 lbs	
1. Test substance	6	6	2.0 /5X	4.0/5X	4
2. Vehicle control	6	6	2.0 /5.6X	4.0/5.6X	4

Data taken from pp. 12-13, 16-17, MRID 45097001.

^a Treatments were given on study days 0, 7, 14, and 21.

C. Dose selection rationale

The study was conducted as a limit test using 5 times the label specified, the recommended dose volume. The product was dosed according to weight in the following pre-measured dose volumes: 0.4 mL for cats weighing ≤ 9 lbs (4.1 kg) and 0.8 mL for cats weighing > 9 lbs. (4.1kg). The vehicle control group received the vehicle at dose volumes equal to 5 times the recommended use volumes of the test substance, which are equivalent to 5.6 times the usual use volumes of the vehicle. The product is intended for once a month use; however, the label states that "if re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly." The study therefore included repeated treatments at weekly intervals for a total of four treatments.

D. Experimental design

The cats were observed daily during study days -14 through -1 (the acclimation period), and twice daily during study days 0 through 37 except on dosing days, when the animals were observed once prior to dosing and 4 times, approximately 1 hour apart, following dosing. These observations included evaluation of the "clinical condition" of the eyes,

appetite, feces, respiration, behavior changes, locomotion and musculature, skin, including dermal irritation, and any signs of vomiting. Physical examinations were conducted prior to the acclimation period and on study days -1 and 37. Body weights were recorded on study days -14, -7, -1, 13, 28, and 37. Food consumption was evaluated once daily during the acclimation period and twice daily during the study except on dosing days, when it was evaluated 5 times; in all cases, a daily summary of food consumption was also made. The amount of food consumed was estimated visually and scored as 1, 2, or 3, indicating, respectively, that greater than or equal to 75%, 25-75%, or less than 25% of the food was consumed; however, the quantity of food the animals were given was not provided in the report.

E. Pathological parameters

Baseline blood samples were collected on study days -7 and -1, and post-treatment blood samples were collected on study days 1, 22, and 37. The report did not mention the venipuncture sites used or whether the animals were fasted overnight prior to blood collection. Due to clotting of some blood samples, it was necessary to collect and test additional samples. Where necessary, study day 1 sampling and testing were repeated on study 8, study day 22 blood sampling and testing were repeated on day 23, and study day 37 blood sampling and testing were repeated on study days 41 and 42. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)*		
X	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

<u>X</u>	ELECTROLYTES	<u>X</u>	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*		Total Cholesterol
X	Potassium*	X	Globulin*
X	Sodium*	X	Glucose*
	ENZYMES	X	Total and direct bilirubin*
X	Alkaline phosphatase(ALK)*	X	Total serum protein (TP)*
	Cholinesterase(ChE)		Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)	X	Albumin/Globulin ratio
X	Serum alanine amino- transferase (also SGPT)*	X	Calcium/phosphorus ratio
X	Serum aspartate amino- transferase(also SGOT)*	X	Blood urea nitrogen/creatinine ratio
	Gamma glutamyl transferase(GGT)	X	Sodium/potassium ratio
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F Statistics

Baseline clinical pathology values were calculated for each animal by averaging the pre-treatment measurements, and study day -1 body weights were used as baseline. Body weight data were analyzed by first comparing the baseline body weights of the two groups by sex with a two-sample t-test. Body weight changes from baseline were calculated for each post-treatment day (study days 13, 20, 28, and 37), and body weight changes were then analyzed by sex with a repeated measure analysis of covariance including terms for Group, Animal (random), Day, and Group*Day interaction with baseline body weight as the covariate. Clinical pathology data were analyzed using a multivariate repeated measures ANOVA, including terms for Group, Sex, Animal (random), Day, and Group*Day interaction. If the Sex effect was statistically significant at the 0.10 level, the data were analyzed by sex with a multivariate repeated measures ANOVA including terms for Group, Animal (random), Day, and Group*Day interaction. If the Group*Day interaction was statistically significant at the 0.10 level, the data were graphed to investigate the nature of the Group by Day interaction, and the data for each study day were compared with normal ranges.

G. Disposition of animals

Not reported.

H. Compliance

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. Exposure levels

Each 1.0 mL of the product contained 100 mg of imidacloprid and 10 mg of pyriproxyfen. For thirty days efficacy, the minimum desired efficacious dose for imidacloprid is 10 mg/kg, and the desired minimum efficacious dose for pyriproxyfen is 0.5 mg/kg. In terms of desired minimum efficacious doses in mg/kg, the exaggerated doses used in the study ranged from 4.92X to 9.57X for imidacloprid and 9.84X to 19.13X for pyriproxyfen.

B. Mortality

There were no deaths during the study.

C. Clinical signs

Clinical observations are summarized in Table 2. Within an hour following the initial treatment on study day 0, four cats in the test substance group and one cat in the vehicle control group were observed to be salivating, and at two hours post dosing all had recovered. The study author stated that "all the cats that salivated were due to licking the test material." Two males in the test substance group vomited, one on study day 19 and the other on study day 25. Two males in the vehicle control group had loose stools, one on study days 18 and 20, and the other on study day 33. One cat in the vehicle control group was observed to be unsteady and circling during the p.m. observation period on study day 23. By the a.m. observation period on study day 24, he had recovered but exhibited a rough hair coat condition at the application site. No mention was made of the study veterinarian examining this animal during the time he was exhibiting symptoms. On study days 14 and 21, rough hair coat was noted at the application sites of all cats of both groups 1-4 hours post dosing, and, on study day 21, one female from the test substance group was pruritic at one hour after dosing, with recovery by 2 hours after dosing. There were no observations of erythema, edema, or alopecia at the application sites. One cat in the vehicle control group exhibited ocular discharge on study day -9 (during acclimation) and study day 16; since this condition occurred both before and after treatment, it is unlikely to be treatment related.

TABLE 2. Clinical observations of cats treated with Imidacloprid/Pyriproxyfen Spot-on Formulation		
Treatment group	Day	Observation
1. Test substance	0	Salivation in 3 males and 1 female within an hour of dosing
	14	Rough hair coat condition at the dose site in 6 males and 6 females at the post dosing observation periods at 1-4 hours post dosing
	16	Ocular discharge in one female cat at the a.m. observation period ^a
	19	Vomiting by one male cat (#762) at the a.m. observation period
	21	Rough hair coat condition at the dose site in 6 males and 6 females at the post dosing observation periods at 1-4 hours post dosing; Pruritis in one female at 1 hour post dosing
	25	Vomiting by one male cat (#758) at the p.m. observation period
2. Vehicle control	0	Salivation in one female within an hour of dosing
	14	Rough hair coat condition at the dose site in 6 males and 6 females at the post dosing observation periods at 1-4 hours post dosing
	18	Loose stools in one male cat (#764)
	20	Loose stools in one male cat (#764)
	21	Rough hair coat condition at the dose site in 6 males and 6 females at the post dosing observation periods at 1-4 hours post dosing
	23	One male (#744) was circling and unsteady at the p.m. observation
	24	Rough hair coat condition at the dose site in one male (#744)
	33	Loose stools in one male cat (#749)

Data taken from Tables 6A and 6B, pp. 34-35, MRID 45097001.

^a This cat also exhibited ocular discharge on study day -9, during acclimation.

D. Bodyweight and weight gain

Individual body weights of the cats fluctuated throughout the acclimation and treatment periods, with no consistent pattern being observed. Mean body weights of both groups, with the sexes both combined and separated, increased at each consecutive weighing from study day -1 to study day 37. There were no significant differences between groups for post-treatment changes in body weight

E. Food consumption

All of the cats on the study generally consumed greater than or equal to 75% of their food. One female (#750) in the test substance group consumed between 25 and 75% of her food on study days -13, 12, 15-17, 19, and 30-33. One female (#751) in the vehicle control group consumed between 25 and 75% of her food on study days 13, 14, 16-18, 31-32. Three additional cats from the test substance group and one cat from the vehicle control group consumed 25-75% of their food for 1-3 days. Cat number 744 from the vehicle control group, who was observed to be circling and unsteady on study day 23, consumed less than 25% of his food on study day 22 and 25-75% of his food on study days 23 and 24. All of the previously mentioned animals consumed greater than or equal

to 75% of their food during the remainder of the pre-treatment and treatment intervals. The study report did not include the quantities of food the cats were fed.

F. Hematology

Nine of the samples submitted for complete blood count and three of the samples submitted for coagulation measurements were could not be analyzed due to clotting. Additional samples were collected and tested as follows: study day 1 sampling and testing were repeated on study day 8; study day 22 sampling and testing were repeated on study day 23; and study day 37 sampling and testing were repeated on study days 41 and 42. Statistical analyses were conducted both with and without the data from the repeated tests, and wherever statistical significance was present without data from the repeated tests, it was also present when the data from the repeated tests was included. The individual results from these repeated tests were omitted from the study report although these data were included in calculating means and standard deviations. Statistically significant ($p < 0.10$) Group by Day interactions were found for the following parameters: platelet counts for males, erythrocyte counts for females, and activated partial thromboplastin times, leukocyte, eosinophil, and lymphocyte counts, and mean corpuscular volumes for the pooled sexes. These values are given in Table 3. These values were all within pre-treatment ranges, and the changes were considered to be spontaneous in nature and unrelated to treatment.

On study day 22, cat #744 (the cat that was observed to be circling and unsteady on study day 23) exhibited an increased hematocrit, erythrocyte count, and hemoglobin concentration. These values were all outside the pre-treatment ranges for these parameters. (See G. Clinical chemistry below.)

TABLE 3. Hematology and coagulation parameters in cats treated with Imidacloprid/Pyriproxyfen Spot-on Formulation which exhibited statistically significant ($p < 0.10$) Changes, Group by Day interactions *								
Parameter	1. Test substance				2. Controls			
	Baseline	Day 1 ^c	Day 22 ^d	Day 37 ^e	Baseline	Day 1 ^c	Day 22 ^d	Day 37 ^e
Males								
Platelets ($10^6/\mu\text{L}$)	0.33	0.26	0.34	0.39	0.30	0.29	0.34	0.33
Females								
Erythrocytes ($10^6/\mu\text{L}$)	9.71	8.73	8.48	8.85	8.46	7.86	8.35	8.65
Pooled Sexes								
Activated partial thromboplastin time (sec)	12.68	13.03	12.21	12.28	13.53	12.80	12.94	13.34
MCV (fl)	41.33	41.19	41.34	41.47	42.81	43.08	43.27	42.85
Leukocytes ($10^3/\mu\text{L}$)	15.05	14.84	11.44	11.99	13.74	15.07	13.12	10.24
Eosinophils ($10^3/\mu\text{L}$)	0.81	1.10	0.43	0.43	0.93	0.90	0.65	0.39
Lymphocytes ($10^3/\mu\text{L}$)	6.22	5.44	4.04	5.13	4.68	4.63	3.87	3.26

Data taken from Tables III.1 and III.2, pp. 81-82, MRID 45097001

* Mean values

^b Baseline values are the means of results from study days -7 and -1.

^c Means for complete blood count (CBC) parameters include data from Day 8 for one female.

^d Means for CBC parameters include data from Day 23 for one male.

^e Means for CBC parameters include data from Day 40 or 41 for two males and two females.

^f Means for CBC parameters include data from Day 8 for two females and one male. Means for coagulation parameters include data from Day 8 for one female.

^g Means for CBC parameters include data from Day 23 for one female

^h Means for coagulation parameters include data from Day 40 or 41 for one male.

G. Clinical chemistry

Statistically significant ($p < 0.10$) Group by Day interactions were found for the following clinical chemistry parameters: alkaline phosphatase and BUN/Creatinine ratio in males. These values were within the pretreatment ranges, and the changes were considered to be spontaneous in nature and unrelated to treatment.

On study day 22, cat #744 (the cat that was observed to be circling and unsteady on study day 23) exhibited increased sodium concentration and total protein; both these values exceeded the pre-treatment ranges. There were also slight increases in his BUN on study

days 1 and 37 and creatinine. These findings in conjunction with those mentioned above (see F. Hematology) are consistent with hemoconcentration due to dehydration.

TABLE 4. Clinical chemistry parameters in cats treated with Imidacloprid/Pyriproxyfen Spot-on Formulation which exhibited statistically significant ($p < 0.10$) Group by Day interactions *								
Parameter	1. Test substance				2. Controls			
	Baseline	Day 1	Day 22	Day 37	Baseline	Day 1	Day 22	Day 37
Males								
Alkaline phosphatase activity (u/L)	52.92	48.33	48.50	45.50	48.92	52.00	53.17	39.00
BUN/creatinine ratio	18.86	18.43	17.56	19.60	18.29	18.33	19.77	18.73

Data taken from Tables III.1, p. 8t, MRID 45097001.

* Mean values

H. Necropsy findings

Necropsies and histopathological examinations were not performed, as all animals survived until termination of the study, and no animals displayed clinical signs which were considered to warrant necropsy.

IV. DISCUSSION

- A. Treatment related clinical signs included salivation and a rough hair coat appearance at the treatment site. Four cats from the test group and one from the control group exhibited salivation after the first treatment. Salivation was first noted within an hour of dosing and ended before the 2 hour post-treatment observation period. The study author attributed the salivation to the animals licking the test substance or vehicle. A rough hair coat appearance at the application site was noted for all cats in both groups on study days 14 and 21 during all post-treatment observations, and one animal from the test group was pruritic at one hour post dosing on study day 21. Clinical signs that may have been related to treatment included vomiting by two cats in the test group and loose stools from two cats in the (vehicle) control group. Additionally, one male from the control group exhibited inappetence on study days 22-24 and was observed to be circling and unsteady at the p.m. observation period on day 23. Clinical chemistry and hematology findings from this cat on day 22 were consistent with hemoconcentration due to dehydration (elevated hematocrit, erythrocyte count, hemoglobin, BUN, creatinine, sodium, and total protein), but since this cat was apparently not given a physical examination, it is unknown whether he was clinically dehydrated, febrile, or presenting neurological deficits. His behavior and appetite were normal for the remainder of the study, as were his clinical pathology parameters. There were no other treatment related effects on hematology, coagulation, and clinical chemistry parameters. There were no

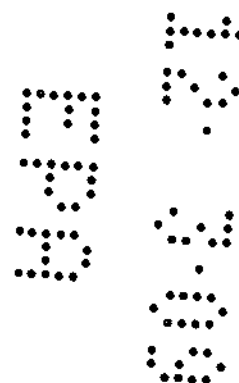
treatment related effects on body weights or food consumption, and there was no evidence of irritation at the application sites. Since the cat that exhibited inappetence, circling, and unsteadiness following the fourth treatment was in the control group, these clinical signs were clearly not due to toxic effects from the active ingredients of the product; however, they may represent toxic effects from an ingredient in the vehicle. The animal was not examined more closely. However, the signs were transient, and the animal apparently recovered with no clinical signs for the remainder of the study and no abnormal physical examination findings on study day 37. The guideline only requires a single re-treatment with observation of the animals to continue only 14 days beyond treatment if no clinical signs of toxicity are noted. As the clinical signs in question did not occur until day 22, (exactly 15 days after the second treatment and were exhibited by an animal from the vehicle control group), they are not considered to be a treatment related.

B. Study deficiencies

An animal on the study exhibited clinical signs which needed a thorough examination to determine the possible cause of such clinical signs.

Due to clotting of some blood samples, it was necessary to collect and test additional samples. Where necessary, study day 1 sampling and testing were repeated on study 8, study day 22 blood sampling and testing were repeated on day 23, and study day 37 blood sampling and testing were repeated on study days 41 and 42. Individual data from the repeated tests were not included in the study report. The guideline requires clinical pathology testing 24 hours after treatment with additional assessment on day 7 if the day 1 results are altered. It is unclear why the tests on day 1 were not repeated until day 8.

Appendix 8



Doug
Spilker/SHAWN/AGCHEM/U
S/BAYER

12/04/2008 02:57 PM

To davis.kable@epa.gov
cc Jennifer
Schofield/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOT
ES, Dan
Ciszewski/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOT
ES, Terry
McNamara/SHAWN/AGCHEM/US/BAYER@BAYER-US-NO
TES
bcc Ernst
Heinen/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES
Subject Domestic Animal Safety Study on Kittens - Decision 400153

Dear Mr. Davis,

Reference is made to the Agency's review, dated November 20, 2008, of the domestic animal safety study protocol (EPA File Symbol No. PR-27997; MRID 47540901) for the proposed product imidacloprid plus pyriproxyfen for use on cats and kittens. The cover letter from you, dated November 21, 2008, indicated that the protocol was deemed acceptable with the two following provisions:

1. "EPA Guidelines 870.7200 specifies that at least six animals per sex should be used at each dosage level"

Bayer Response: As described in the Agency's protocol review, the study protocol will be amended to require that all treatment groups contain 12 animals (six male and six female) as tested in two replicates:

- 5x negative control substance (mineral oil) = six animals (three per gender) per replicate (12 total)
- 3x vehicle control substance = six animals (three per gender) per replicate (12 total)
- 5x vehicle control substance = six animals (three per gender) per replicate (12 total)
- 3x test substance = six animals (three per gender) per replicate (12 total)
- 5x test substance = six animals (three per gender) per replicate (12 total)

The randomization section of the protocol will be appropriately modified to reflect this change.

2. "Coagulation times are not needed as these data are available from adult cats and can be used."

Bayer Response: The testing of coagulation times will be removed from the protocol per the Reviewer's recommendation.

Additional Item: Also in the review (Item No. 1, page 2 of 5), TRB commented that "No information [was] given as to the percentages of the active ingredients and/or inerts in this formulation." This need was also expressed in a telephone call by the Agency (K. Davis to D. Spilker), on November 19, 2008. In response, Bayer sent the Agency (email dated Nov. 19, 2008) the Confidential Statement of Formula for the proposed product. In explanation, the citation in the Appendix of the proposed protocol was merely a "placeholder" for inserting the Certificate of Analysis on the test article actually used in the study.

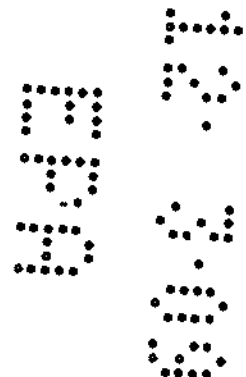
With Bayer Animal Health's above agreement to revise the protocol appropriately according to the Agency's review, and the providing of the proposed formula, it is our understanding that this protocol would be considered acceptable to the Agency. The protocol will ultimately be included as a part of the final domestic animal safety study report. However, it is unclear whether the Agency would like to have a copy of the aforementioned amended protocol for their files prior to the conduct of the study. Please respond with your desire for this, and whether any of the above understandings are incorrect.

Best regards,
Douglas A. Spilker

Doug Spilker, Ph. D.
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ANIMAL HEALTH
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Email: doug.spilker.b@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Powered by People, Driven by Science"





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Douglas A. Spilker
Bayer HealthCare, LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390

NOV 21 2008

Dear Dr. Spilker:

Subject: Protocol; Domestic Animal Safety Study on Kittens
Imidacloprid + Pyriproxyfen Spot-on
Date Submitted: September 12, 2008



The Agency has reviewed the submitted protocol for the conduct of a domestic animal safety study on kittens (MRID 47540901) using an imidacloprid + pyriproxyfen spot-on product. The Agency's review (D356838) dated November 20, 2008, was deemed acceptable with the following provisions:

1. EPA Guidelines 870.7200 specifies that at least six animals per sex should be used at each dosage level. In addition, the guidelines also state the vehicle control should be administered at a 5X level. The Agency strongly recommends that a total of 12 animals be dosed with the 5X vehicle control substance. Please see attached review for further detail.
2. Coagulation times are not needed as these data are available from adult cats and can be used. The listing of hematology and clinical chemistry parameters that will be measured is appropriate. Please see attached review for further detail.

A copy of the Agency review has been enclosed for your records. Should you have any questions regarding this letter, please contact me at (703) 306-0415.

Sincerely,

Kable Bo Davis
Entomologist
Insecticide-Rodenticide Branch
Registration Division (7505P)

Enclosure- Agency Review (D356838)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

CONTAINS CONFIDENTIAL BUSINESS INFORMATION

November 20, 2008

MEMORANDUM

Subject: Subject: Domestic Animal Safety Study on Kittens
 EPA Reg. No. /File Symbol: PR-27997
 DP Barcode: DP 356838
 Decision No.: 400153
 Action Code: R272
 PC Codes: N/A

From: Byron T. Backus, Ph.D., Toxicologist
 Technical Review Branch
 Registration Division (7505P)

Byron T. Backus
11-20-2008
BMC

To: Kable Davis/Venus Eagle, RM 01
 Insecticide-Rodenticide Branch
 Registration Division (7505P)

Registrant: BAYER HEALTHCARE LLC

FORMULATION FROM LABEL:

N/A

ACTION REQUESTED: The Risk Manager requests:

"...Please review the attached domestic animal protocol for kittens. The proposed spot-on will contain a mixture of imidacloprid and pyriproxyfen. In addition to the study, I also included a copy of the cover letter which explains everything..."

BACKGROUND:

The material received for review includes a document (assigned MRID 47540901) titled:
"Evaluation of the General Safety of Imidacloprid + Pyriproxyfen Spot-On in 8-Week-Old Kittens."

COMMENTS AND RECOMMENDATIONS:

TRB's comments are listed below:

1. No information is given as to the percentages of active ingredients and/or inerts in this formulation. Currently, the registrant has a registered product (EPA Reg. No. 11556-116) with a label declaration of 9.1% imidacloprid as sole active; this product is a spot-on for use on cats and kittens 8 weeks of age or older.

2. Two kitten safety studies were submitted to support the registration of 11556-116. These studies were reviewed by Virginia Dobozy in a memorandum dated 9/23/97. The following are the executive summaries of these two studies:

i. In a domestic animal safety study (MRID #44157301), six 6 week-old kittens/sex were treated with AdvantageTM (9.1% imidacloprid) at 5X the recommended use rate (2.0 mL). Six kittens/sex were also treated with the vehicle control at the recommended use rate (0.4 mL). According to the study protocol, the animals were supposed to receive 8 treatments at weekly intervals. However, two males and two females in the imidacloprid-treated group died or were euthanized within 72 hours after the first treatment. On necropsy, the two females had suppurative cholangiohepatitis which was assumed to be due to an ascending bacterial infection in the liver. In addition, one female had mild diffuse lipidosis. There were no remarkable findings in the males. The study protocol was revised to test the toxicity of the major vehicle excipient. Three six week-old female kittens were treated with the vehicle at 5X the recommended use rate. All three died within 24 hours of treatment. The study report concluded that the kittens were stressed from weaning and were not able to tolerate 5X the recommended use rate.

The study is considered **unacceptable and cannot be upgraded**. It was terminated prior to completion due to animal welfare considerations.

ii. In a domestic animal safety study (MRID #44157302), six 8 week-old kittens/sex were treated with AdvantageTM (9.1% imidacloprid) at 5X the recommended use rate (2.0 mL) at weekly intervals for eight treatments. Six kittens/sex were treated with the vehicle control at the recommended use rate (0.4 mL) at weekly intervals for eight treatments. There was no evidence of treatment-related toxicity in clinical signs or clinical pathology parameters. All animals gained weight during the study. It was demonstrated that 8 week-old kittens can tolerate a dose of 5X the recommended use rate.

The study is considered **acceptable and satisfies the draft guideline requirement (81-6) for a domestic animal safety study**.

Three six week-old female kittens died after treatment with the vehicle at 5X the recommended use rate in the study in MRID #44157301. From the DER for this study: "The study report states that the death of the vehicle-treated kittens substantiated that the major excipient induced the toxicity observed in the AdvantageTM-treated kittens." No deaths among the vehicle control kittens occurred in the study in MRID 44157302, but these animals were only treated at the 1X (0.4 mL) dose level.

3. From p. 6 of MRID 47540901 the study will be conducted in two equivalent replicates. Each replicate will include the following:

5x negative control substance (mineral oil) = six animals (three per gender) per replicate

3x vehicle control substance = four animals (two per gender) per replicate.

5x vehicle control substance = four animals (two per gender) per replicate.

3x test substance = six animals (three per gender) per replicate.

5x test substance = six animals (three per gender) per replicate.

This gives a total of 8 animals (four per gender) for the 5x vehicle control substance. The 870.7200 Guidelines specify that: "At least six animals per sex should be used at each dosage level." In addition, the Guidelines state that: "The vehicle control should be administered at a 5X level. The vehicle should contain the inert ingredients at the maximum levels that would appear in the 5X formulation." TRB strongly recommends that a total of 12 animals be dosed with the 5X vehicle control substance. If there is a limit to the number of animals that are used in this study then the total number of animals in the 5X negative control substance (mineral oil) group can be reduced to eight animals (four animals per replicate). The absence of a 1X group is noted; however, if no effects are observed in the 3X test substance group then this should be no problem.

4. From p. 10 of MRID 47540901 it is stated that kittens will be prophylactically treated against coccidiosis in the period during the acclimation period (specifically days -14 to -10). TRB would have no objections to the treatment of the kittens with drugs up to day -3 to minimize the possibility that they would show effects from protozoan infestations during the treatment period. From p. 13 all kittens will be treated with fenbendazole and sulfadimethoxine on days 3 to 7; if the need for additional treatment becomes necessary a facility veterinarian, the study director and sponsor representative would agree with the selection "so as to avoid the use of medications and/or therapies that either enhance or diminish the pharmacological effects of the test substance. However, if necessary, emergency treatment will be given immediately to any animal and the sponsor representative will be notified as soon as possible." This is acceptable to TRB.

5. From information on p. 12 a 1X dosage of the test substance would be 0.23 mL, and a 1X dosage of the vehicle control would be 0.21 mL. The 3X and 5X applications would then be multiples of these quantities. The total dose will be divided by three and will be administered as 3 subdoses approximately 60 minutes apart. The applications will be made directly to the skin on the dorsal midline from the base of the skull to the interscapular region. These dosage rates and type of application are acceptable.

6. In order to minimize stress on the animals, 1-3 mL [per kitten] of blood will be collected from the animals on study days -7, 1, 15 and 28. Coagulation times are not needed as these data are

available from adult cats and can be used. The listing (p. 16) of hematology and clinical chemistry parameters that will be measured is appropriate.

7. TRB has no objections or concerns regarding the rest of the proposed protocol.

21-Day Screen Completed by
Contractor

21-Day Expires on 12-24-09

Jacket # 11556-RLN
MRID# 479248

Content Screen: Recommended to
Pass/Fail

86-5 Review: Passed/Failed/NA

Transfer This Jacket to:

LINDA ARRINGTON

Memorandum

11536-RLN

Went on

Prizlet

CS

Date: 12/10/09

To: PM 01, Regulatory Manager

From: Information Services Branch, ITRMD

Your receipt of this data submission is not an indication that MRIDs for the enclosed studies have been posted to OPPIN.

We expect that it will be approximately 5 days from the above date before the study-level data is available in OPPIN.

If you have any questions about this process, please contact Teresa Downs (305-5363).

This is a: ☒ fully accepted submission
☐ partially accepted submission
☐ rejected submission



ADMINISTRATIVE NO(S).: 11556-RLN

PM: /

CHEMICAL NO.: _____

The jacket for this action can be
requested through the JACKETS system.

PRIA 2 – 21 Day Content Screen Review Worksheet

(EPA/OPP Use Only)

3/23/09

21 Day Screen Start Date: 12-3-09

Experts In-Processing Signature: M F Harrington Date 12-4-09

Fee Paid: Yes ☒

Division management contacted on issues No ☐ Yes ☐ Date _____

EPA Reg. Number: <u>11556-RLN</u>		EPA Receipt Date: <u>12-3-09</u>				
Items for Review			Yes	No	N/A*	
1	Application Form (EPA Form 8570-1)(link to form) signed & complete including package type			X		
2	Confidential Statement of Formula all boxes completed, form signed, and dated (EPA Form 8570-4) (Link to form) a) All inerts (link to http://www.epa.gov/opprd001/inerts/), including fragrances, approved for the proposed uses (see Footnote A)			X		
		yes	no			
		X				
3	Certification with Respect to Citation of Data (EPA Form 8570-34) (Link to form) completed and signed (N/A if 100% repack) Certificate and data matrix consistent			X		
	If applicant is relying on data that are compensable, is the offer to pay statement included. (see Footnote B)			X		
	If applicable, is there a letter of Authorization for exclusive use only.					
4	Formulator's Exemption Statement (EPA Form 8570-27) (Link to form) completed and signed (N/A if source is unregistered or applicant owns the technical)			X		
5	Data Matrix (EPA Form 8570-35) (Link to form) both internal and external copies (PR 98-5) (Link to PR 98-5) completed and signed (N/A if 100% repack) a) Selective Method (Fee category experts use) b) Cite-All (Fee category experts use) c) Applicant owns all data (Fee category experts use)			X		
		yes	no			
		X				
6	5 Copies of Label (link to http://www.epa.gov/oppfead1/labeling/lrm/) (Electronic labels on CD are encouraged and guidance is available)(link to http://www.epa.gov/pesticides/regulating/registering/submissions/index.htm#labels)			X		

7	Is the data package consistent with PR Notice 86-5 (link to PRN 86-5)	X		
8	Notice of Filing (link to http://www.epa.gov/pesticides/regulating/tolerance_petitions.htm) included with petitions (link to http://www.epa.gov/pesticides/regulating/tolerances.htm)			X
9	If applicable for conventional applications, reduced risk rationale (link to http://www.epa.gov/opprd001/workplan/reducedrisk.html)			X
10	Required Data (link to http://www.epa.gov/pesticides/regulating/data_requirements.htm) and/or data waivers. See Footnote C.			
	a) List study (or studies) not included with application			

Comments:

11C ☐ Studies associated w/ jacket have not passed 86-5 review. (Correction sent in)

Jacket Passed

MRID 479248

* N/A – Not Applicable

Footnotes

A. During the 21 day initial content review, all CSFs will be reviewed to determine whether all inerts listed, including fragrances, are approved for the proposed uses. If an unapproved inert is identified, the applicant must either 1) resolve the inert issue by, for example, removing the inert, substituting it with an approved inert, submitting documentation that EPA approved the inert for the proposed pesticidal uses, correcting mistakes on the CSF, etc. or 2) provide the data to support OPP approval of the inert or 3) withdraw the application. Removing or substituting an inert ingredient will require a new CSF and may require submission of data. All information, forms, data and documentation resolving the inert issue must have been received by the Agency or the application withdrawn within the 21 day period, otherwise, the Agency will reject the application as described below.

To successfully complete this aspect of the 21 day initial content screen, applicants are **strongly encouraged** to verify that all inert ingredients have been approved for the application's uses even if a product is currently registered by consulting the inert Web

site [link to <http://www.epa.gov/opprd001/inerts/lists.html>] and if the inert is not approved, to **obtain the necessary inert approval prior to submitting an application to register a pesticide product containing that inert ingredient.** Some inert ingredients are no longer approved for food uses or certain types of uses. The name and/or CAS number on a CSF must match the name and CAS number on this web site. Simple typographical errors in the name or CAS number have resulted in processing delays.

If an inert is not listed on the inert ingredient web site and the applicant believes that the inert has been approved, the applicant should contact the Inert Ingredient Assessment Branch (IIAB) at inertsbranch@epa.gov and resolve the issue. Copies of the correspondence with IIAB resolving the issue should accompany the application. All new inerts except PIP inerts are reviewed by IIAB. The IIAB should also be contacted for any questions on what supporting data needs to be submitted for and the Agency's inert review process. Questions on PIP inerts should be directed to the Chief of Microbial Pesticides Branch [Link to http://www.epa.gov/oppbopd1/biopesticides/contacts_bppd.htm].

When a brand, trade, or proprietary name of an inert ingredient is listed on a CSF, additional information such as an alternate name of the inert, CAS number or other information [link to <http://www.epa.gov/opprd001/inerts/tips.pdf>] must also be included to enable the Agency to determine if it has been approved. Each component of an inert mixture (including a fragrance) must be identified. In some cases, the supplier of the mixture or fragrance may need to provide this information to the Agency. Prior to the Agency's receipt of an application, applicants must arrange with a proprietary mixture or fragrance supplier to provide the component information to the Agency or promptly upon EPA's request. If the inert ingredients in a proprietary blend (including fragrances) cannot or are not identified or provided within the 21-day content review period, the Agency will reject the application.

During the 21 day content review, applicants should submit information to the individual identified by the Agency when the applicant is informed of an unapproved inert.

Unapproved Inerts Identified on CSFs

All applications except conventional new products and PIPs

Once an unapproved inert is identified on a CSF, the Agency will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or
2. Submit the information and data needed for the Agency to approve the unapproved inert. If this option is selected and implemented, the Agency may request an extension in the PRLA decision review timeframe to accommodate the inert review/approval process;

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of these options is selected and implemented by the applicant within the 21 day content review period, the Agency will reject the application and retain 25% of the full fee of the category identified.

Conventional New Product Applications

When the Registration Division identifies an unapproved inert on a CSF with an application for a new product that the applicant has not identified as requiring an inert approval (R311, R312 or R313), it will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or
2. Submit the information and data needed for the Agency to approve the unapproved inert, including any required petition to establish or amend a tolerance or exemption from a tolerance. (This option may change the PRIA category for the application, which could require a longer decision review time and a larger fee. If additional fees are due, they must be received by the Agency within the 21 day content review period.)
3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21-day content-review period, the Agency will reject the application and retain 25% of the appropriate fee for the new product-inert approval category.

PIP Applications

When the Biopesticide and Pollution Prevention Division identifies an unapproved inert on a PIP CSF and a request to approve the inert does not accompany the application, it will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the spelling or name of the inert to that in 40 CFR 174, or providing documentation that the inert has been approved; or
2. Submit the information and data needed for the Agency to approve the unapproved inert. If an inert ingredient tolerance exemption petition is required, the petition must be received by the Agency and the B903 fee paid within the 21 day period. If this option is selected and implemented, the Agency will discuss harmonizing the timeframe for both actions.

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21 day content review period, the Agency will reject the application and retain 25% of the fee.

B. A policy on documentation of offers to pay is still being developed, however, for a me-too or fast track (similar/identical) new product, R300 or A530, an application without the necessary authorizations of offers to pay will be placed into either R301 or A531. The Agency recommends that authorizations of offers to pay be submitted with other PRIA applications to avoid delays in the Agency's decision.

C. Biopesticide applicants are advised to contact the Agency and discuss study waivers prior to submitting their application to the Agency. Documentation of such discussions should be submitted with the study waiver.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 4, 2009

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OPP Decision Number: D-424201
EPA File Symbol or Registration Number: 11556-RLN
Product Name: ADVANTAGE IGR 5
EPA Receipt Date: 03-Dec-2009
EPA Company Number: 11556
Company Name: BAYER HEALTHCARE LLC

DOUGLAS A. SPILKER, PH.D.
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

SUBJECT: Receipt of Registration Application Subject to Registration Service Fee

Dear Registrant:

The Office of Pesticide Programs has received your application and certification of payment. If you submitted data with this application, the results of the PRN-86-5 screen will be communicated separately. During the administrative screen, the Office of Pesticide Programs has determined that this Action is subject to a Pesticide Registration Service Fee as defined in the Pesticide Registration Improvement Act.

The Action has been identified as Action Code: R310

NEW PRODUCT;NON-FAST TRACK (INCLUDES REVIEWS OF PRODUCT
CHEMISTRY;ACUTE TOXICITY;PUBLIC HEALTH PEST EFFICACY);

No additional payment is due at this time.

If you have any questions, please contact the Pesticide Registration Service Fee
Ombudsman at (703) 305-6249.

Sincerely,
Front End Processing Staff
Information Technology & Resources Management Division

A large, stylized handwritten signature in black ink, likely belonging to a representative of the EPA, is written over the typed name and title.

Fee for Service

{863543+~

This package includes the following

☒ New Registration

☐ Amendment

☒ Studies? ☐ Fee Waiver?

☐ volpay % Reduction: ____

for Division

☐ AD

☐ BPPD

☒ RD

Risk Mgr.

Receipt No.

S-

863543

EPA File Symbol/Reg. No.

11556-RLN

Pin-Punch Date:

12/3/2009

☐ This item is NOT subject to FFS action.

Action Code:

Requested:

R310

Granted:

R310

Amount Due: \$

4578⁰⁰

Inert approved. S. Rock 12/4/09

Parent/Child Decisions:

☒ Inert Cleared for Intended Use

☐

Uncleared Inert in Product

Reviewer:

[Signature]

Date:

12/04/09

Remarks:

Online Payment

Online Payment

Step 3: Confirm Payment

1 | 2 | 3

Thank you.

Your transaction has been successfully completed.

Pay.gov Tracking Information

Application Name: PRIA Service Fees

Pay.gov Tracking ID: 2501ICHP

Agency Tracking ID: 74089837114

Transaction Date and Time: 11/23/2009 12:03 EST

Payment Summary

Address Information

Account Holder Name: Douglas A. Spilker
Billing Address: 12707 Shawnee
Mission Parkway
Billing Bayer Animal
Address 2: Health
City: Shawnee
State / Province: KS
Zip / Postal Code: 66216-1846
Country: USA

Account Information

Card Type: Master Card
Card Number: *****0576
Decision Number:
Registration Number:
Company Bayer HealthCare,
Name: LLC-AHD
Company Number: t1556
Action Code: R310

Payment Information

Payment Amount: \$4,578.00
Transaction Date 11/23/2009
and Time: 12:03 EST



United States
Environmental Protection Agency
Washington, DC 20460

☒ Registration
☐ Amendment
☐ Other

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number 11556-XXX <u>RLN</u>	2. EPA Product Manager Venus Eagle	3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted
4. Company/Product (Name) Advantage IGR 5	PM# 01	
5. Name and Address of Applicant (Include ZIP Code) Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390 <input type="checkbox"/> Check if this is a new address	6. Expedited Review. In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to: <input checked="" type="checkbox"/> EPA Reg. No. _____ Product Name _____	

Section - II

<input type="checkbox"/> Amendment - Explain below.	<input type="checkbox"/> Final printed labels in response to Agency letter dated _____
<input type="checkbox"/> Resubmission in response to Agency letter dated _____	<input type="checkbox"/> "Me Too" Application.
<input type="checkbox"/> Notification - Explain below.	<input checked="" type="checkbox"/> Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Application for new product registration; Proposed Fee Category: R310 - "New end-use or manufacturing-use product; requires review of data package within RD." Fee category recommended by V. Eagle (PM01). See attachment (Bpp.) for more information.
Contact: doug.spilker.b@bayer.com

Section - III

1. Material This Product Will Be Packaged In:				2. Type of Container	
Child-Resistant Packaging <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Unit Packaging <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Water Soluble Packaging <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		<input checked="" type="checkbox"/> Metal	
* Certification must be submitted				<input checked="" type="checkbox"/> Plastic	
If "Yes" Unit Packaging wgt. No. per container		If "Yes" Package wgt. No. per container		<input checked="" type="checkbox"/> Glass	
				<input checked="" type="checkbox"/> Paper	
				Other (Specify) _____	
3. Location of Net Contents information <input checked="" type="checkbox"/> Label <input type="checkbox"/> Container		4. Size(s) Retail Container 4-0.23mL tube		5. Location of Label Directions <input type="checkbox"/> On Label <input checked="" type="checkbox"/> On Labeling accompanying product	
6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled		<input checked="" type="checkbox"/> Other See attachment			

Section - IV

1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)		
Name Douglas A. Spilker, Ph.D.	Title Manager, EPA Reg. Affairs	Telephone No. (include Area Code) 913-268-2751
Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment both under applicable law.		8. Date Application Received (Stamped)
2. Signature 	3. Title Manager, EPA Reg. Affairs	
4. Typed Name Douglas A. Spilker, Ph.D.	5. Date 30 Nov. 2009	

ATTACHMENT FOR OPP
APPLICATION FOR PESTICIDE NOTIFICATION

Advantage® IGR 5

With this application and the enclosed documents, Bayer HealthCare, Animal Health Division, requests the registration of Advantage® IGR 5, a new spot-on insecticide product for use on small cats and kittens. This imidacloprid + pyriproxyfen-containing product will be packaged in single-use tubes for application by pet owners and veterinarians for control of various stages of fleas and lice on cats and kittens.

Although this is an application for registration of a *new* product, the product itself is not really new to the Agency. In explanation, on December 11, 2007, the Agency issued Notices of Registration for both *Advantage Plus 9 for Cats* (EPA Reg. No. 11556-126) and *Advantage Plus 18 for Cats* (EPA Reg. No. 11556-129); see Appendix 1. The proposed product contains the identical formulation and use pattern, residential - indoor, as the previously accepted products Advantage Plus 9 and 18. Although Bayer HealthCare subsequently voluntarily withdrew the registrations of *Advantage Plus 9* and *Advantage Plus 18*, this was for marketing reasons, and not because of a safety/risk issue or lack of data for the products. Therefore, much of the data needed to support this proposed product has already been reviewed and accepted by the Agency during the review process for the Advantage Plus 9 and 18. Furthermore, there are analogous registrations for this identical formulation for use on dogs and puppies, currently registered as *Advantage Plus 10* (EPA Reg. No. 11556-128), *Advantage Plus 20* (11556-125) *Advantage Plus 55* (11556-127) and *Advantage Plus 100* (11556-130).

Product Chemistry

The insecticide formulation is identical to the formulation previously accepted for the imidacloprid + pyriproxyfen-containing cat products (Advantage Plus 9 and 18), as well as the currently registered dog spot-on products (Advantage Plus 10, 20, 55 and 100). Therefore, the product chemistry data requirements have already been satisfied for this formulation.

Briefly, the insecticide formulation is a liquid solution of imidacloprid (9.1% w/w) and pyriproxyfen (0.46% w/w) in inert ingredients which are on EPA's list of acceptable inert ingredients for use in pesticides. The source of the active ingredients for this product are

[REDACTED] The product chemistry data to support the registration of this formulation are in the following Bayer Reports which are on file with the Agency, and listed in the Data Matrix:

Bayer Report No. 75133 entitled "Product Chemistry of (10% w/v, 9.1% w/w) Imidacloprid + (0.5% w/v, 0.46% w/w) Pyriproxyfen Topical Solution – OPPTS 830 – Group A: Product Identity, Composition, and Analysis," EPA MRID No. 45096902,

Bayer Report No. 75132 entitled "Product Chemistry of (10% w/v, 9.1% w/w) Imidacloprid + (0.5% w/v, 0.46% w/w) Pyriproxyfen Water Topical Solution, OPPTS 830 Group B – Physical/Chemical Properties," EPA MRID No. 45096903, and,

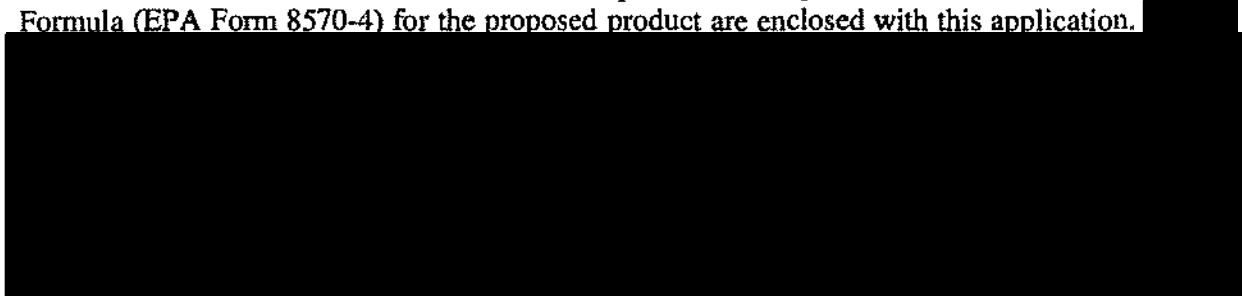
Bayer Report No. 75130 entitled "Validation of Bayer Animal Health Test Method TMC-14.02 for the Determination of Imidacloprid and Pyriproxyfen Topical Solution Formulation by HPLC," EPA MRID No. 45096901.

Although the report titles do not use the "Advantage® IGR" trade name, the formulation described and tested is identical to Advantage® IGR 5.

Also, these three product chemistry reports support the registration of the two other pending Advantage® IGR products [Advantage® IGR 9 and Advantage IGR 18] whose applications accompany this application.

The Agency has previously reviewed these product chemistry data and found them acceptable and fulfilling all product chemistry requirements, except for the Storage Stability data requirement and some minor Confidential Statement of Formula (CSF) issues (see Appendix 2). The CSF issues are moot, since new proposed CSFs are included in this application. Bayer agreed to provide the stability data on the product using final packaging. This study is on-going, with a due date to the Agency 5/31/2010; an interim report of the study was sent to the Agency on 7/2/09 (see Appendix 3.)

Confidential Statement of Formula - Two copies of the respective Confidential Statement of Formula (EPA Form 8570-4) for the proposed product are enclosed with this application.



Product Toxicology

We are relying on the previously accepted acute toxicity studies on the formulation to support this proposed registration action; that is, no new acute toxicity data are included with the application. The Precautionary Label Language and Signal Word are the same as the currently EPA-accepted *Advantage Plus for Dog* products. Because the acute oral toxicity value for the formulation was below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP).

To support the registration of Advantage® IGR 5 (and also for the other two Advantage® IGR products), the following acute toxicology data were submitted with the original applications for the Advantage Plus registration sent April 10, 2000.

<u>EPA MRID Number</u>	<u>EPA Guideline Number</u>	<u>Bayer Report Number</u>	<u>Bayer Report Title</u>
45096904	870.1100	75195	Acute Oral Toxicity Study with Imidacloprid (9.1%) /Pyriproxyfen (0.9%) Spot On in Rats
45096905	870.1200	75196	Acute Dermal Toxicity Study with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in Rats
45096906	870.1300	75197	Acute 4-Hour Inhalation Toxicity Study with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in Rats
45096907	870.2400	75199	Primary Eye Irritation Study in Rabbits with Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On
45096908	870.2500	75200	Primary Dermal Irritation Study in Rabbits with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On
45096909	870.2600	75201	Dermal Sensitization Study in Guinea Pigs – Closed Patch Technique with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On

Please note, the study titles refer to test materials with a slightly different formulation than that which is proposed for registration. The formulation proposed for registration contains 9.1% imidacloprid, 0.46% pyriproxyfen, and [REDACTED], and the other inert ingredients identified on the Confidential Statement of Formula. The formulation used for five of the acute toxicity studies contained 9.1% imidacloprid and a higher pyriproxyfen concentration (0.9%) and [REDACTED]. The formulation used for the primary eye irritation study (Bayer Report No. 75199, EPA MRID No. 45096907) contained 9.1% imidacloprid, 0.9% pyriproxyfen, and [REDACTED]

[REDACTED] In a November 2, 1999 meeting between EPA and Bayer representatives, the Agency's technical reviewers (Byron Backus and John Redden) confirmed that EPA would accept these studies since the formulation tested represents a "worst case" compared to the current formulation proposed for registration.

The Agency reviewed these six studies (review dated August 30, 2000; see Appendix 4). All six studies were classified as "Acceptable" by the Agency and have fulfilled the acute toxicology requirements necessary for registration. Based on the results of these six acute toxicity studies,

the Agency concluded that the product would be a Toxicity Category III product with a CAUTION signal word. The enclosed draft labeling reflects this signal word.

The results of the acute oral toxicity study (Bayer Report No. 75195; EPA MRID No. 45096904) were an LD₅₀ of 1283 mg/kg for male rats and 1000 mg/kg for female rates. As these values were below the 1500 mg/kg threshold level, and as this is a residential use, the Agency specified the product must be in child-resistant packaging (CRP). Bayer conducted a follow-up acute oral toxicity study (Bayer Report No. 75922; MRID No. 47089411) with the proposed final end-use formulation (9.1% imidacloprid, 0.46% pyriproxyfen, and [REDACTED]) to confirm if this product must be in child-resistant packaging. The estimated oral LD₅₀ for female rats in this study is 1098 mg/kg, and again below the 1500 mg/kg threshold for child-resistant packaging. Therefore, we understand that the Advantage[®] IGR products must be sold in child-resistant packaging (CRP) to receive registration from the Agency. Data from CRP testing is enclosed with this action and is discussed below.

Packaging

This product will consist of a blister package constructed of plastic and foil containing individual single-use plastic tubes each containing 0.23 mL of the liquid insecticide. For this product there will only be one package size – a 4-tube package. The plastic and foil blisters will be marketed inside cardboard boxes. The boxes will contain all of the appropriate text from the enclosed draft labeling, dated 11/24/09. The complete label text, including directions for use, will be in a leaflet insert that will accompany the blister package in the cardboard box. The individual plastic tubes inside the blisters will contain only the draft labeling indicated on page 8 of the label text. Please note, because the tubes are very small in size, we are proposing that only the product name, the active ingredients, the amounts of the active ingredients and the EPA Reg. No. be printed onto each tube. This packaging and labeling scheme is identical to that used by Bayer's currently registered product, Advantage[®] 9 Topical Solution (EPA Reg. No. 11556-116).

Child-Resistant Packaging Testing

The most significant difference in the packaging between the previously registered products - *Advantage Plus 9* and *Advantage Plus 18* - and the proposed products is that the products are in a different Child-Resistant Packaging (CRP) material. For the previous products, the CRP packaging was made of PVC and the respective child and adult testing data were found acceptable to the Agency. The proposed products will be produced in KISI blisters. The testing design to satisfy the requirements for all product presentations was developed with the agreement of the Agency's expert, Dr. Rosalind Gross (see Appendix 5.) The end results of these efforts are that Bayer has developed CRP (KISI Type) blister packaging for 4-tube blisters for the Advantage IGR 5. The Child-Resistant Packaging tests have been conducted by Great Lakes Marketing, Toledo, Ohio, using both children and senior panel tests according to the Agency guidance and the effectiveness specifications in 16 CFR Part 1700.15 (b) for child-resistant (special) packaging.

Details of the child-resistant and senior adult panel tests for the 4-tube blister package are included in the following enclosed two reports to support the registration of Advantage® IGR 5 for cats and kittens:

Bayer Report No. 33741 (4-pack; child panel)

Bayer Report No. 33742 (4-pack; adult panel)

A CRP Certification letter is also enclosed.

With regard to the overall CRP testing of the various packaging configurations, Bayer is aware of PR Notice 97-9 regarding the electronic submission of CRP test data, and therefore these data have been prepared appropriately and are included on separate CDs with this application.

Efficacy

To support the efficacy claims for the Advantage® IGR 5 (as well as Advantage IGR 9 and 18) product(s) on cats, Bayer is citing studies previously reviewed and accepted by the Agency for Bayer's currently registered imidacloprid-containing Advantage® 9 Topical Solution (EPA Reg. No. 11556-116) and Advantage® 18 Topical Solution (EPA Reg. No. 11556-118) products. The Advantage IGR formulation contains 100 mg imidacloprid per 1.0 mL of product. Based on previous research, the minimum effective dosage of imidacloprid for control of fleas and lice is 10 mg AI/kg (~4.5 mg AI/lb.) body weight. Therefore, this single-use tube of product (volume 0.23 mL) when applied to cats and kittens up to 5 lbs. in weight (label limitation), provides the appropriate and identical effective rate as the aforementioned Advantage products. Therefore, the previously submitted data are relevant and support this application for registration. Specifically, these reports are:

EPA MRID 43679503 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Cats" (Bayer Report No. 74571) and,

EPA MRID 43679504 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Cats" (Bayer Report No. 74581).

EPA MRID 43679609 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Dogs" (Bayer Report No. 74572) and,

EPA MRID 43679610 entitled "Efficacy Confirmation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Dogs" (Bayer Report No. 74541).

The above referenced studies support the once-per-month use of imidacloprid (Advantage®) to control fleas and, therefore, the once-per-month use of imidacloprid in Advantage® IGR to control fleas.

The currently accepted labels for Advantage® 9 and 18 Topical Solution and the draft proposed labels for Advantage® IGR 5, 9 and 18 have a claim for water resistance of the product (i.e.

waterproof), larvicidal efficacy, and a 12-hour "speed of kill" claim. These claims are supported by Bayer studies previously submitted to, reviewed by, and accepted by the Agency for Bayer's currently registered products Advantage® 9 Topical Solution (EPA Reg. No. 11556-116) and Advantage® 18 Topical Solution (EPA Reg. No. 11556-118). Specifically, these reports are:

EPA MRID 44256903 entitled "Evaluation of the Effects of Shampooing or Water Immersion on the Initial and Residual Efficacy of Advantage® for Flea Control on Dogs" (Bayer Report No. 74792),

EPA MRID 44256902 entitled "Imidacloprid Topical Formulation: Larvicidal Effect against *Ctenocephalides felis* in the Surroundings of Treated Dogs" (Bayer Report No. 74828) and,

EPA MRID 44256901 entitled "Comparative Evaluation of How Quickly Advantage® and Frontline™ (fipronil) Top Spot Kill Fleas on Dogs" (Bayer Report No. 74800).

Whereas Advantage® is efficacious against larval and adult fleas, the new Advantage® IGR product is effective against flea larvae, adult fleas, and flea eggs. The active ingredient, pyriproxyfen, is currently registered in numerous products for many different uses. Among these registrations, there are at least 13 currently registered pyriproxyfen flea products which range in active ingredient concentration from 0.125 to 5.3 percent. The concentration of pyriproxyfen in Advantage® IGR (0.46%) falls within the range of concentrations of the currently registered products.

Bayer is also citing three efficacy studies with pyriproxyfen from McLaughlin Gormley King Co. (MGK) with the appropriate MRID numbers. Enclosed with these applications is an authorization letter from MGK to permit the use of these data to support the Advantage® IGR products. Specifically, these reports are:

EPA MRID No. 450860801 entitled "Evaluation of Two Concentrations of Nylar (Pyriproxyfen) in a Dip and Shampoo Formulation Against the Hatch of Flea Eggs Collected from Treated Cats" (MGK Report No. OT018-94),

EPA MRID No. 450860801 "Flea Eggs: Target of the New IGR On-Animal Treatments" (MGK Report No. OT016-93),

EPA MRID No. 450860801 "Final Report on Comparison of Isopropyl Alcohol Dilutions of Pyriproxyfen and Fenoxycarb on Hatchability of Flea Eggs" (MGK Report No. OT006-96) and,

Please note that "Nylar" is a trade name for pyriproxyfen.

The results of these studies support the once-a-month application rate for Advantage® IGR since the efficacious concentration of pyriproxyfen used in the studies was lower than the concentration in the formulation proposed for registration. In addition, the lower concentration of pyriproxyfen was shown to be effective for a period greater than one month.

These efficacy study reports also support the registration of the other Advantage® IGR products for cats - Advantage® IGR 9 and 18 - whose application accompanies this application.

The only other pest that appears on the proposed label is biting (chewing) lice. To support these claims, we reference the efficacy data (Bayer Report No. 75950; MRID No. 47190401) previously used to support lice control for the *Advantage Plus for Dogs* product. The report is referenced in the Data Matrix. These data show that the imidacloprid-containing Advantage is very effective for the control of the dog louse (*Trichodectes canis*); see Appendix 6. The dog louse and the louse infesting cats (*Felicola subrostratus*) are very similar in that they are both considered "biting" lice. Therefore, the imidacloprid in the Advantage IGR formulation should also be very effective for control of the cat louse, and we have received anecdotal reports via our 1-800 line that imidacloprid is effective against cat lice, when treating for fleas.

Companion Animal Safety

Adult Cats - Bayer has on file with the Agency Report No. 75122 (*Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation in the Target Species, Adult Cats*) to demonstrate the safety of Advantage IGR in adult cats. The report was assigned EPA MRID No. 45097001 and underwent Agency review. The EPA concluded that the report was "Acceptable" and that the study adequately addressed the safety requirements contained in Guideline 870.7200: *Companion Animal Safety* (see Appendix 7). Furthermore, the study supports a 7-day retreatment interval.

The aforementioned report (EPA MRID No. 45097001) also supports the pending registration of Advantage IGR 9 and IGR 18 which accompany this submission.

Kittens - A series of three companion animal studies collectively demonstrated the safety of the imidacloprid + pyriproxyfen formulation in kittens 9 weeks of age and older. However, to support a more desirable use pattern on the label allowing treatment of 8-week old kittens, a new domestic animal safety study was conducted (Bayer Report No. 33714), using a protocol submitted to and accepted by the Agency, with agreed to minor modifications (see Appendix 8.) Bayer Report No. 33714 is being submitted with this application for registration of the Advantage IGR 5.

Product Labeling

Enclosed for Agency acceptance are five (5) copies of draft labels, dated 11/24/09, for Advantage® IGR 5. This label is very similar to the previously stamped-accepted label for Advantage Plus 9 (EPA Reg. No. 11556-126; see Appendix 1). The label for the proposed product differs from the previously registered Advantage Plus product in the following areas:

1. Appropriate label language to propose a minimum age restriction (8-weeks) on kittens;
2. Broadening the bulleted list of marketing claims

3. Revising the HOW TO OPEN section to include more information since the product will now be sold in a different Child-Resistant Packaging. These were the directions used in the CRP testing.
4. Recommendation for the control of biting (chewing) lice.

Data Compensation

An appropriate data matrix listing all of the data necessary to support the registration of Advantage® IGR 5 (and also Advantage® IGR 9 and 18) is enclosed with this application. Please note, the enclosed data matrix cites only those data necessary for this registration. This registration application is for a product used only on cats (classified as an indoor, residential use); the data matrix does not cite any imidacloprid environmental fate, ecological effects or residue chemistry data because these data are not necessary for this proposed registration.

Generic Data

With regard to **imidacloprid**, Bayer CropScience LP (BCS) is the basic registrant of imidacloprid. BCS and Bayer HealthCare LLC (BHC) are wholly owned subsidiaries of Bayer Corporation, and therefore, the BHC, Animal Health Division, cannot claim Formulator's Exemption for the generic data requirements. Accordingly, enclosed is a copy of Letter of Authorization from Bayer CropScience (EPA Company No. 264) authorizing the use of the generic imidacloprid data by Bayer HealthCare LLC, Animal Health Division (EPA Company No. 11556). These generic data are cited in the enclosed data matrix.

With regard to **pyriproxyfen**, a completed Formulator's Exemption form (EPA Form 8570-27) is enclosed with this initial application for Bayer to address compensation of pyriproxyfen generic data. Also, enclosed is a Letter of Authorization from Sumitomo Chemical Company Ltd.

Product Specific Data

All of the data necessary to support the registration of Advantage® IGR 5 are data previously submitted by Bayer's Animal Health group (EPA Company No. 11556) or are enclosed with this application or were submitted by the McLaughlin Gormley King Co. (MGK). Enclosed with this application is a Letter of Authorization from MGK. All of these data are cited in the enclosed data matrix.

Enclosed is also a completed Certification with Respect to Citation of Data (EPA Form 8570-34) indicating we are choosing the Selective Method of Support for pyriproxyfen efficacy data. Again, a Letter of Authorization from MGK to cite these data is enclosed.

Bayer HealthCare
Animal Health



Via Federal Express

November 30, 2009

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle
Registration Division

Subject: Applications for the Registration of
Advantage® IGR 5 (Agency Tracking #74089836606),
Advantage® IGR 9 (Agency Tracking #74089836904), and
Advantage® IGR 18 (Agency Tracking #74089837114)
products for pest control on cats and kittens

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Ms. Eagle:

Enclosed with this cover letter are applications for registration of three (3) new companion animal spot-on products, named *Advantage IGR 5*, *Advantage IGR 9*, and *Advantage IGR 18*, and all the appropriate supporting documents and data. These imidacloprid + pyriproxyfen-containing products will be packaged in single-use tubes for application by pet owners and veterinarians for control of various stages of fleas and lice on cats and kittens. The purpose of this cover letter is to provide an explanatory overview of the submission which may aid in the processing of the enclosed information and respective registration applications.

Although these are applications for registration of *new* products, the products themselves are not really new to the Agency. On December 11, 2007, the Agency issued Notices of Registration for both *Advantage Plus 9 for Cats* (EPA Reg. No. 11556-126) and *Advantage Plus 18 for Cats* (EPA Reg. No. 11556-129). The proposed three products contain the identical formulation and use pattern, residential - indoor, as the previously accepted products of *Advantage Plus 9* and *18*. Although Bayer

HealthCare subsequently voluntarily withdrew the registrations of *Advantage Plus 9* and *Advantage Plus 18*, this was for marketing reasons, and not because of a safety/risk issue or lack of data for the products. Therefore, much of the data needed to support these proposed products have already been reviewed and accepted by the Agency during the review process for the *Advantage Plus 9* and *18*. Furthermore, there are analogous registrations for this identical formulation for use on dogs and puppies, currently registered as *Advantage Plus 10* (EPA Reg. No. 11556-128), *Advantage Plus 20* (11556-125) *Advantage Plus 55* (11556-127) and *Advantage Plus 100* (11556-130).

Applications for three (3) new products are enclosed and include *Advantage IGR 9* (0.4 mL tube), *Advantage IGR 18* (0.8 mL tube) and a third product, *Advantage IGR 5*, especially designed for small cats and kittens in a smaller single-use tube (0.23 mL). These products only differ from one another in terms of different dose/container sizes for different sizes of cats and kittens (see Table 1.)

Product Chemistry: The insecticide formulation is identical for all three of the proposed products, and is identical to the formulation previously accepted for the imidacloprid + pyriproxyfen-containing cat products (*Advantage Plus 9* and *18*), as well as the currently registered dog spot-on products (*Advantage Plus 10*, *20*, *55* and *100*). Therefore, the product chemistry data requirements have already been satisfied for this formulation. Appropriate Confidential Statements of Formula for the three proposed products are enclosed.

Efficacy: All of the products control fleas. These products are similar to the imidacloprid-containing *Advantage* products (*Advantage 9 Topical Solution*, EPA Reg. No. 11556-116; *Advantage 18 Topical Solution*, EPA Reg. No. 11556-118), except a small amount (0.46%) of a very effective insect growth regulator, pyriproxyfen, has been added to enhance efficacy against flea eggs. Whereas *Advantage* was efficacious against larval and adult fleas, the new combination product is effective against flea larvae, adult fleas, and flea eggs. Since the data, as listed in the data matrix, to support the flea control claims for this formulation have been reviewed and accepted by the Agency under the previous *Advantage Plus 9* and *Advantage Plus 18* actions, no new flea efficacy data are being submitted with this application. You will also note that the proposed labels contain many of the flea control claims found on the stamped-accepted labels for

Advantage Plus 9, Advantage Plus 18, as well as, on the stamped-accepted labels for *Advantage Plus 10, Plus 20, Plus 55 and Plus 100 for Dogs*.

The only other pest that appears on the proposed labels is the biting (chewing) louse. To support these claims, we reference the efficacy data previously submitted for lice control under the *Advantage Plus for Dogs* product, which is referenced in the Data Matrix.

Application Method and Weight Bands: The method of application is the same for all three products, and it is the same application method as for the currently registered *Advantage Topical Solution* products. The entire contents of the appropriate-sized tube are applied to cats or kittens to a localized area on the neck at the base of the skull to control fleas. One product, *Advantage IGR 5*, will treat cats and kittens weighing 5 lbs. or less in size. The dose for this product is 0.23 mL of solution in a plastic tube. The second product - *Advantage IGR 9* - will treat cats and kittens weighing 5 to 9 lbs. with a tube size of 0.4 mL. The third product - *Advantage IGR 18* - will treat cats weighing 9 lbs. and greater in size, with a tube size of 0.8 mL of solution in a plastic tube. All three tubes have different label colors to easily distinguish them from one another.

Acute Toxicity Studies: As discussed earlier, the insecticide formulation is the same for all three proposed products (and the currently registered dog products). We are relying on the previously accepted acute toxicity studies on the formulation to support these proposed registration actions; that is no new acute toxicity data are included with the applications. The Precautionary label language and Signal Word are the same as the currently EPA-accepted *Advantage Plus for Dog* products. Because the acute oral toxicity value for the formulation was below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP).

Packaging: The packaging for the proposed cat products will be identical to the packaging used with the currently registered *Advantage* products for cats (EPA Reg. Nos. 11556-116 and -118) except that the tubes will be in a Child-Resistant blister. The packaging for the cat products will consist of a cardboard box with all appropriate label text except for the full directions for use. Inside the box will be a leaflet containing all the label text. Also inside the box will be a CRP blister package containing 4 or 6 tubes of the appropriate size.

The most significant difference in the packaging between the previously registered products - *Advantage Plus 9* and *Advantage Plus 18* - and the proposed products is that the products are in a different Child-Resistant Packaging (CRP) material. For the previous products, the CRP packaging was made of PVC and the respective child and adult testing data were found acceptable to the Agency. The proposed products will be produced in KISI blisters. The packaging material scheme for all three of the proposed registrations is similar, and the CRP testing data for the various sizes are enclosed. The testing design to satisfy the requirements for all product presentations was developed with the agreement of the Agency's expert, Dr. Rosalind Gross. CRP certification letters are also enclosed.

With regard to the overall CRP testing of the various packaging configurations, Bayer is aware of PR Notice 97-9 regarding the electronic submission of CRP test data, and therefore these data have been prepared appropriately and are included on CDs.

Companion Animal Safety: Submitted in support of the previously accepted registrations for *Advantage Plus 9* for Cats and Kittens (EPA Reg. No. 11556-126) and for *Advantage Plus 18* for Cats (EPA Reg. No. 11556-129), Bayer has an appropriate domestic animal safety study on file with the Agency that demonstrates the safety of *Advantage IGR* on adult cats. The EPA concluded that the report was "Acceptable" and that the study adequately addressed the safety requirements contained in Guideline 870.7200: *Companion Animal Safety*. Furthermore, the study supports a 7-day retreatment interval. To support a label allowing treatment of 8-week old kittens, enclosed is a new domestic animal safety study (Bayer Report No. 33714) conducted using a protocol submitted to and accepted by the Agency.

Data Compensation: An appropriate data matrix listing all of the data necessary to support the registration of *Advantage IGR 5*, *Advantage IGR 9* and *Advantage IGR 18* is enclosed with this application. Please note, the enclosed data matrix cites only those data necessary for this registration. This registration application is for a product used only on cats (classified as an indoor, residential use); the data matrix does not cite any imidacloprid environmental fate, ecological effects nor residue chemistry data because these data are not necessary for this proposed registration.

Generic Data - With regard to **imidacloprid**, Bayer CropScience LP (BCS) is the basic registrant of imidacloprid. BCS and Bayer HealthCare

Ms. Venus Eagle
Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency

Page 5
November 30, 2009

LLC (BHC) are wholly owned subsidiaries of Bayer Corporation, and therefore, the BHC, Animal Health Division, cannot claim Formulator's Exemption for the generic data requirements. Accordingly, enclosed are copies of a Letter of Authorization from Bayer CropScience (EPA Company No. 264) authorizing the use of the generic imidacloprid data by Bayer HealthCare LLC, Animal Health Division (EPA Company No. 11556). These generic data are cited in the enclosed data matrix. With regard to pyriproxyfen, a completed Formulator's Exemption form (EPA Form 8570-27) is enclosed with this initial application for Bayer to address compensation of pyriproxyfen generic data. Also, enclosed is a Letter of Authorization from Sumitomo Chemical Company Ltd.

Product Specific Data - All of the data necessary to support the registration of *Advantage IGR 5*, *Advantage IGR 9* and *Advantage IGR 18* are data previously submitted by Bayer's Animal Health group (EPA Company No. 11556) or are enclosed with this application or were submitted by the McLaughlin Gormley King Co. (MGK). Enclosed with this application is a Letter of Authorization from MGK. All of these data are cited in the enclosed data matrix. Enclosed is also a completed Certification with Respect to Citation of Data (EPA Form 8570-34) indicating we are choosing the Selective Method of Support for pyriproxyfen efficacy data. Again, a Letter of Authorization from MGK to cite these data is enclosed.

I hope this overview cover letter is helpful in processing the attached applications. If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely,



Douglas A. Spilker, Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker.b@Bayer.com

DAS/lt

Enclosures

Table 1.

Product Name	Animal	Animal Size	Tube Size (fl. oz.)	No. of Tubes Per Package
Advantage [®] IGR 5 (EPA File Symbol 11556-XXX)	Cats and Kittens	≤ 5 lbs.	0.0078 (0.23 mL)	4
Advantage [®] IGR 9 (EPA File Symbol 11556-XXX)	Cats and Kittens	5 to 9 lbs.	0.014 (0.4 mL)	4 or 6
Advantage [®] IGR 18 (EPA File Symbol 11556-XXX)	Cats and Kittens	≥ 9 lbs.	0.027 (0.8 mL)	4 or 6

Transmittal Document

1. Name and Address of Submitter

Bayer HealthCare LLC
Animal Health Division
Box 390
Shawnee Mission, Kansas 66201-0390



Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs
(913) 268-2751

2. Regulatory Action in Which this Package is Submitted

Data submitted to support the proposed registration of Advantage® IGR 5 (EPA File Symbol 11556-XXX)

3. Transmittal Date

November 30, 2009

4. List of Submitted Studies:

MRID No. Volume

- 1 - "Evaluation of the General Safety of M881," 40 CFR Parts 160 and 792, T. J. Madsen, Report No. 33714, 193 p.
- 2 - "Child-Resistant Packaging (CRP) Child Panel Test of 4 x 0.23 mL Advantage® IGR KISI Blisters for Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, L. M. Dixon, Report No. 33741, 59 p.
- 3 - "Child-Resistant Packaging (CRP) Senior Adult Panel Test of 4 x 0.23 mL Advantage® IGR KISI Blisters for Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, L. M. Dixon, Report No. 33742, 251 p.

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Enclosures:

Advantage IGR 5

- 1 copy Advantage IGR 5 Application for Pesticide Registration with Application Attachment and five Appendices:
 - Appendix 1 – Advantage Plus 9 and 18 Registration Notices & Voluntary Cancellations
 - Appendix 2 – Product Chemistry Review
 - Appendix 3 – Storage Stability Extension and Interim Report
 - Appendix 4 – Acute Toxicity Study Reviews
 - Appendix 5 – CRP Correspondence
 - Appendix 6 – Lice Study Review
 - Appendix 7 – Companion Animal Safety Study Review
 - Appendix 8 – Companion Animal (kitten) Protocol Review
- 1 copy proof of PRIA payment
- 5 copies draft labels, date of draft 11/24/09
- 1 copy Letter of Authorization from MGK
- 1 copy Letter of Authorization from Bayer CropScience
- 1 copy Letter of Authorization from Sumitomo
- 1 copy CRP Certification letter
- 1 copy Formulator's Exemption (8570-27)
- 1 copy Certification with Respect to Data (8570-34)
- 1 copy data matrix (confidential)
- 1 copy public data matrix
- 2 copies Confidential Statement of Formula
- 3 copies data transmittal document
- 3 copies Bayer Report No. 33714 (Domestic Animal Safety – Kittens)
- 3 copies Bayer Report No. 33741 (Child Resistant Packaging Study; 4-pack/child)
- 3 copies Bayer Report No. 33742 (Child Resistant Packaging Study; 4-pack/adult)
- 1 copy CD transmittal document
- 1 CD (electronic data file) for Bayer Report No. 33741
- 1 CD (electronic data file) for Bayer Report No. 33742

Form approved. OMB No. 2070-0060, 2070-0057, 2070-0107, 2070-0122, 2070-0164.



United States
Environmental Protection Agency
Washington, DC 20460
Formulator's Exemption Statement
(40 CFR 152.85)

Applicant's Name and Address Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201	EPA File Symbol/Registration Number 11556-XXX
	Product Name Advantage IGR 5
	Date of Confidential Statement of Formula (EPA Form 8570-4) 11/20/2009

As an authorized representative of the applicant for registration of the product identified above, I certify that:

(1) This product contains the following active ingredient(s):

pyriproxyfen

imidacloprid (not citing Formulator's Exemption for this active ingredient)

(2) Of these, each active ingredient listed in paragraph (4) is present solely as the result of the use of that active ingredient in the manufacturing, formulation or repackaging another product which contains that active ingredient which is registered under FIFRA Section 3, is purchased by us from another person and meets the requirements of 40 CFR section 158.50(e)(2) or (3).

(3) Indicate by checking (A) or (B) below which paragraph applies:

☐ (A) An accurate Confidential Statement of Formula (EPA FORM 8570-4) for the above identified product is attached to this statement. That formula statement indicates, by company name, registration number, and product name, the source of the active ingredient(s) listed in paragraph (1).

OR

☒ (B) The Confidential Statement of Formula (CSF)(EPA Form 8570-4) referenced above and on file with the EPA is complete, current, an accurate and contains the information required on the current CSF.

(4) The following active ingredients in this product qualify for the formulator's exemption.

Source		
Active Ingredient	Product Name	Registration Number
pyriproxyfen	[REDACTED]	[REDACTED]
Signature 	Name and Title D.A. Spilker, EPA Reg. Affairs Mgr	Date 30 Nov 2009

EPA Form 8570-27 (Rev. 06-2004)

Copy 1 - EPA
Copy 2 - Applicant copy



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
1200 Pennsylvania Avenue, N.W.
WASHINGTON, D.C. 20460

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 1.25 hours per response for registration and 0.25 hours per response for reregistration and special review activities, including time for reading the instructions and completing the necessary forms. Send comments regarding burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden to: Director, Collection Strategies Division (2822T), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, N.W., Washington, DC 20460. Do not send the completed form to this address.

Certification with Respect to Citation of Data

Applicant's/Registrant's Name, Address, and Telephone Number Bayer HealthCare LLC, Animal Health Div. POB 390, Shawnee Mission, KS 66201 (913-268-2751)	EPA Registration Number/File Symbol 11556-XXX
Active Ingredient(s) and/or representative test compound(s) Imidacloprid, pyriproxyfen	Date 30 Nov 2009
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158) Indoor, residential	Product Name Advantage IGR 5

NOTE: If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulator's Exemption Statement (EPA Form 8570-27).

☐ I am responding to a Data-Call-In Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

SECTION I: METHOD OF DATA SUPPORT (Check one method only)

☐ I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

☒ I am using the selective method of support (or cite-all option under the selective method), and have included with this form a completed list of data requirements (the Data Matrix form must be used).

SECTION II: GENERAL OFFER TO PAY

[Required if using the cite-all method or when using the cite-all option under the selective method to satisfy one or more data requirements]

☒ I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA.

SECTION III: CERTIFICATION

I certify that this application for registration, this form for reregistration, or this Data-Call-In response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses.

I certify that for each exclusive use study cited in support of this registration or reregistration, that I am the original data submitter or that I have obtained the written permission of the original data submitter to cite that study.

I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (i) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.

I certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.

I certify that the statements I have made on this form and all attachments to it are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

Signature

Douglas A. Spilker

Date

30 Nov 2009

Typed or Printed Name and Title

Douglas A. Spilker, EPA Reg. Affairs Manager



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 0.25 hours per response for registration activities and .025 hours per response for information, including suggestions for reducing the burden to: Director, OPPE Information Management Division (2137), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Do not send the form to the address.

DATA MATRIX

Date: November 24, 2009		EPA Reg No./File Symbol: 11556-XXX, 11556-XXX 11556-XXX		Page 1 of 11	
Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390		Product: Advantage® IGR 5 Advantage® IGR 9 Advantage® IGR 18		Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1	
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

Product Chemistry, Section 158.240

61-1	Chemical identity	42055302	264	PER	BR 1759 (TGA1)	
		43306001	264	PER	BR 1879 (TGA1)	
		42256302	264	PER	BR 1766 (Formulation)	
61-2	Statement of Composition	42055302	264	PER	BR 1759 (TGA1)	
		43306001	264	PER	BR 1879 (TGA1)	
		42270801	264	PER	BR 1785 (TGA1)	
61-3	Formation of impurities	42256302	264	PER	BR 1766 (Formulation)	
		42055302	264	PER	BR 1759 (TGA1)	
		42256302	264	PER	BR 1766 (Formulation)	
62-1	Preliminary analysis	42055303	264	PER	BR 1760 (TGA1)	
		43306002	264	PER	BR 1880 (TGA1)	
		42270802	264	PER	BR 1786 (TGA1)	
62-2	Certification of limits	42256302	264	PER	BR 1766 (Formulation)	
		42055303	264	PER	BR 1760 (TGA1)	
		43306002	264	PER	BR 1880 (TGA1)	
62-3	Analytical method	42256302	264	PER	BR 1766 (Formulation)	
		42055303	264	PER	BR 1760 (TGA1)	
		43213001	264	PER	BR 1874 (TGA1)	
		43306002	264	PER	BR 1880 (TGA1)	
		42256302	264	PER	BR 1766 (Formulation)	
		45096901	11556	OWN	Report No. 75130	



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401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 0.25 hours per response for registration activities and .025 hours per response for information, including suggestions for reducing the burden to: Director, OPPE Information Management Division (2137), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Do not send the form to the address.

DATA MATRIX

Date: November 24, 2009		EPA Reg No./File Symbol: 11556-XXX, 11556-XXX 11556-XXX		Page 2 of 11	
Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390		Product: Advantage® IGR 5 Advantage® IGR 9 Advantage® IGR 18		Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1	
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

63-1	Chemical and Physical Properties	42055304	264	PER	BR 1761 (TGAI)	
		42256302	264	PER	BR 1766 (Formulation)	
63-2	Appearance	42055304	264	PER	BR 1761 (TGAI)	
		42256302	264	PER	BR 1766 (Formulation)	
63-3	Physical state	42055304	264	PER	BR 1761 (TGAI)	
		42256302	264	PER	BR 1766 (Formulation)	
63-4	Odor	42055304	264	PER	BR 1761 (TGAI)	
		42256302	264	PER	BR 1766 (Formulation)	
63-5	Melting point	42055304	264	PER	BR 1761 (TGAI)	
63-6	Boiling point	42055304	264	PER	BR 1761 (TGAI)	
63-7	Density	42055304	264	PER	BR 1761 (TGAI)	
		43356302	264	PER	BR 1761 (Formulation)	
63-8	Solubility	42055304	264	PER	BR 1761 (TGAI)	
63-9	Vapor pressure	42055304	264	PER	BR 1761 (TGAI)	
63-10	Dissociation constant					N.A. - Does not dissociate
63-11	Octanol / water partition	42055304	264	PER	BR 1761 (TGAI)	
63-12	pH	42055304	264	PER	BR 1761 (TGAI)	
		42256302	264	PER	BR 1766 (Formulation)	
63-13	Stability	42055304	264	PER	BR 1761 (TGAI)	
63-14	Oxidizing / reducing action		264	PER		N.A. - No oxidative or reductive characteristics
63-15	Flammability	42055304	264	PER	BR 1761 (TGAI)	
63-16	Explosibility	42055304	264	PER	BR 1761 (TGAI)	



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

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DATA MATRIX

Date: November 24, 2009			EPA Reg No./File Symbol: 11556-XXX, 11556-XXX 11556-XXX			Page 3 of 11
Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			Product: Advantage® IGR 5 Advantage® IGR 9 Advantage® IGR 18			Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description

63-17	Storage stability	42055304	264	PER	BR 1761 (TGA1)	
		42256302	264	PER	BR 1766 (Formulation)	
63-18	Viscosity		264	PER		N.A. - Solid
63-19	Miscibility		264	PER		N.A. - Solid
63-20	Corrosion characteristics	42055304	264	PER	BR 1761 (TGA1)	
		42256302	264	PER	BR 1766 (Formulation)	
63-21	Dielectric breakdown volt					N.A. - Solid
64-1	Submittal of samples				Samples available upon request	
830-Group A	Product Chemistry: Identity, Composition, Analysis	45096902	11556	OWN	Report No. 75133	
830-Group B	Product Chemistry: Physical/Chemical Properties	45096903	11556	OWN	Report No. 75132	
Wildlife and Aquatic Organisms, Section 158.490						
71-1	Acute avian oral - quail/duck					N.A.
71-2(a)	Avian dietary - quail					N.A.
71-2(b)	Avian dietary - duck					N.A.
71-3	Wild mammal toxicity					N.A.
71-4(a)	Avian reproduction - quail					N.A.
71-4(b)	Avian reproduction - duck					N.A.
71-5	Simulated or actual field study					N.A.
72-1(a)	Fish toxicity - bluegill					N.A.
72-1(b)	Fish toxicity bluegill - tep					N.A.



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DATA MATRIX

Date: November 24, 2009		EPA Reg No./File Symbol: 11556-XXX, 11556-XXX 11556-XXX		Page 4 of 11	
Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390		Product: Advantage® IGR 5 Advantage® IGR 9 Advantage® IGR 18		Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1	
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

72-2(a)	Invertebrate toxicity - Daphnia					N.A.
72-2(b)	Invertebrate toxicity - Amphipods					N.A.
72-2(c)	Acute aquatic invertebrate toxicity - Chironomids					N.A.
72-3(a)	Estuarine / marine toxicity - fish					N.A.
72-3(b)	Estuarine / marine toxicity - mollusk					N.A.
72-3(e)	Estuarine/marine toxicity - shrimp					N.A.
72-4(a)	Early life stage - fish					N.A.
72-4(b)	Life cycle invertebrate					N.A.
72-7	Simulated or actual field study					N.A.
None	Foliar half-life and distribution for potatoes					N.A.
None	Runoff and Erosion predictions for apple/potato/cotton					N.A.
None	Risk assessment for apple/potato/cotton					N.A.
None	PELMO Modeling - sugarbeet/Germany					N.A.
Toxicology, Section 158.340						
870.1100	Acute oral toxicity rat	42055331	264	PER	Report No. 100040 (TGAI)	
		42256313	264	PER	Report No. 100010 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		43679601	11556	OWN	Report No. 74585 (Adv)	
		45096904	11556	OWN	Report No. 75195 (Adv Plus)	
		47089411	11556	OWN	Report No. 75922 (Adv Plus)	



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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

870.1200	Acute dermal toxicity, rat/rabbit	42055332	264	PER	Report No. 100041 (TGAI)	
		42256315	264	PER	Report No. 100002 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		4379602	11556	OWN	Report No. 74584 (Adv)	
		45096905	11556	OWN	Report No. 75196	
870.1300	Acute inhalation toxicity, rat	42055333	264	PER	Report No. 99806 (TGAI)	
		42286101	264	PER	Report No. 99806-1 (TGAI)	
		42256317	264	PER	Report No. 100012 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		43679603	11556	OWN	Report No. 74589 (Adv)	
870.2400	Primary eye irritation - rabbit	45096906	11556	OWN	Report No. 75197 (Adv Plus)	
		42055334	264	PER	Report No. 99679 (TGAI)	
		42256319	264	PER	Report No. 99815 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		43679604	11556	OWN	Report No. 74588 (Adv)	
		45096907	11556	OWN	Report No. 75199 (Adv Plus)	



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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note	Description
					Report Number	

870.2500	Primary dermal irritation - rabbit	42055335	264	PER	Report No. 99804 (TGAJ)	
		42256321	264	PER	Report No. 99816 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		43679605	11556	OWN	Report No. 74586 (Adv)	
		45096908	11556	OWN	Report No. 75200 (Adv Plus)	
870.2600	Dermal sensitization - guinea pig	42055336	264	PER	Report No. 99800 (TGAJ)	
		42256323	264	PER	Report No. 100003 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		43679606	11556	OWN	Report No. 74587 (Adv)	
		45096909	11556	OWN	Report No. 75201 (Adv Plus)	
81-8(SS)	Acute neurotoxicity	43170301	264	PER	Report No. 106348	
		43285801	264	PER	Report No. 106348-1	
82-1(a)	90-day feeding - rodent	42256327	264	PER	Report No. 100036	
82-1(b)	90-day feeding - non-rodent	42256328	264	PER	Report No. 100176	
82-2	21-day dermal - rabbit/rat	42256329	264	PER	Report No. 100688	
82-5(b)	90 day neurotoxicity - mammal	43286401	264	PER	Report No. 106356	
83-1(a)	Chronic feeding toxicity - rodent	42256331	264	PER	Report No. 100652	
		42256332	264	PER	Report No. 101931	
		42256333	264	PER	Report No. 102658	
		42256334	264	PER	Report No. 99672	



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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

83-1(b)	Chronic feeding toxicity - non-rodent	42273002	264	PER	Report No. 100015	
83-2(a)	Oncogenicity - rat	42256331	264	PER	Report No. 100652	
		42256332	264	PER	Report No. 101931	
		42256333	264	PER	Report No. 102658	
		42256334	264	PER	Report No. 99672	
		42256335	264	PER	Report No. 100693	
83-2(b)	Oncogenicity - mouse	42256336	264	PER	Report No. 101929	
		42256337	264	PER	Report No. 99808	
83-3(a)	Developmental toxicity - rat	42256338	264	PER	Report No. 98571	
83-3(b)	Developmental toxicity - rabbit	42256339	264	PER	Report No. 98572	
83-4	Two generation reproduction - rat	42256340	264	PER	Report No. 100647	
84-2(a)	Gene mutation (ames test)	42256341	264	PER	Report No. 101276	
		42256342	264	PER	Report No. 98584	
		42256343	264	PER	Report No. 98570	
84-2(b)	Structural chromosomal aberration	42256344	264	PER	Report No. 100021	
		42256345	264	PER	Report No. 99262	
		42256346	264	PER	Report No. 99257	
		42256347	264	PER	Report No. 102652	
		42256348	264	PER	Report No. 102654	
		42256349	264	PER	Report No. 102655	



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Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			Product: Advantage® IGR 5 Advantage® IGR 9 Advantage® IGR 18		Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

84-4	Other genotoxic effects	42256350	264	PER	Report No. 99676	
		42256351	264	PER	Report No. 101275	
		42256352	264	PER	Report No. 98573	
		42256353	264	PER	Report No. 102653	
85-1	General metabolism	42256354	264	PER	Report No. 101999	
		42256355	264	PER	Report No. 87264	
		42256356	264	PER	Report No. 87265	
		42256357	264	PER	Report No. 102617	
870.7200 (86-1)	Domestic Animal Safety	43679501	11556	OWN	Report No. 74579 (Adv)	Cats
		43679502	11556	OWN	Report No. 74591 (Adv)	Cats
		44157301	11556	OWN	Report No. 74746 (Adv)	Kittens
		44157302	11556	OWN	Report No. 74747 (Adv)	Kittens
		45097001	11556	OWN	Report No. 75122 (Adv Plus)	
		47089401	11556	OWN	Report No. 75120 (Adv Plus)	
		47089402	11556	OWN	Report No. 75120-1 (Adv Plus)	Addendum to Report No. 75120
		47089403	11556	OWN	Report No. 75190 (Adv Plus)	
		47089404	11556	OWN	Report No. 75190-1 (Adv Plus)	Addendum to Report No. 75190
		47089405	11556	OWN	Report No. 75191 (Adv Plus)	
		47089406	11556	OWN	Report No. 75191-1 (Adv Plus)	Addendum to Report No. 75191
			11556	OWN	Report No. 33714 (M881)	Adv plus/kittens - 0.23 mL Submitted with Advantage IGR 5



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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

95-9	Efficacy	43679503	11556	OWN	Report No. 74571 (Adv)	Cats
		43679504	11556	OWN	Report No. 74581 (Adv)	Cats
		43679609	11556	OWN	Report No. 74572 (Adv)	Dogs
		43679610	11556	OWN	Report No. 74541 (Adv)	Dogs
		44256901	11556	OWN	Report No. 74800 (Adv)	Speed of flea kill
		44256902	11556	OWN	Report No. 47828 (Adv)	Larvicidal efficacy
		44256903	11556	OWN	Report No. 74792 (Adv)	Effects of shampooing
		47109101	11556	OWN	Report No.75867 (K9)	Waterproof
		45086801	1021	PER	Report No. OT018-94	Pyriproxyfen efficacy
		45086801	1021	PER	Report No. OT016-93	Pyriproxyfen efficacy
		45086801	1021	PER	Report No. OT006-96	Pyriproxyfen efficacy
		47190401	11556	OWN	Report No. 75950	Lice
Plant Protection, Section 158.540						
122-2	Aquatic plant growth					N.A.
123-2	Aquatic plant growth					N.A.
Non-Target Insects, Section 158.590						
141-1	Honey bee acute contact					N.A.
141-2	Honey bee residue on foliage					N.A.
Reentry Protection, Section 158.390						
230-236	Mixer/loader/appligator exposure					N. A.
Environmental Fate, Section 158.290						
161-1	Hydrolysis					N.A.
161-2	Photodegradation - water					N.A.



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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

161-3	Photodegradation - soil					N.A.
162-1	Aerobic soil metabolism					N.A.
162-2	Anerobic soil metabolism					N.A.
162-3	Anaerobic aquatic metabolism					N.A.
163-1	Leaching / adsorption/desorption					N.A.
164-1	Terrestrial field dissipation					N.A.
165-1	Confined rotational crop					N.A.
165-2	Field rotational crop					N.A.
166-1	Ground water - small prospective					N.A.
None	Environmental fate summary					N.A.
Residue, Section 158.240						
171-4(a)	Nature of residue - plants					N.A.
171-4(b)	Nature of residue - livestock and poultry					N.A.
171-4(c)	Residue analytical method - plants					N.A.
171-4(d)	Residue analytical method - animal					N.A.
171-4(e)	Storage stability					N.A.
171-4(f)	Magnitude of residues - meat/milk/poultry/egg					N.A.
171-4(g)	Magnitude of residue - crop field trials					N.A.
171-4(h)	Magnitude of residue - processed food/feed					N.A.
171-4(i)	Method validation/ multiresidue method					N.A.
None	Benefits Reports					
None	Dietary Analysis					N.A.



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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

Child-Resistant Packaging, Section 157						
157.20	Standards - Child-Resistant Packaging Testing	47089407	11556	OWN	Report No. 75913	Aclar CRP packaging
		47089408	11556	OWN	Report No. 75914	Aclar CRP packaging
		47089409	11556	OWN	Report No. 75915	Aclar CRP packaging
		47089410	11556	OWN	Report No. 75916	Aclar CRP packaging
		47089103	11556	OWN	Report No. 75897	Aclar CRP packaging
		47089104	11556	OWN	Report No. 75898	Aclar CRP packaging
		47089101	11556	OWN	Report No. 75893	Aclar CRP packaging
		47089102	11556	OWN	Report No. 75894	Aclar CRP packaging
			11556	OWN	Report No. 33733	0.8 mL/4 pk/child (KIS1) - Advantage IGR 18
			11556	OWN	Report No. 33734	0.8 mL/4 pk/adult (KIS1) - Advantage IGR 18
			11556	OWN	Report No. 33735	0.8 mL/6 pk/child (KIS1) - Advantage IGR 18
			11556	OWN	Report No. 33736	0.8 mL/6 pk/adult (KIS1) - Advantage IGR 18
			11556	OWN	Report No. 33737	0.4 mL/4 pk/child (KIS1) - Advantage IGR 9
			11556	OWN	Report No. 33738	0.4 mL/4 pk/adult (KIS1) - Advantage IGR 9
			11556	OWN	Report No. 33739	0.4 mL/6 pk/child (KIS1) - Advantage IGR 9
			11556	OWN	Report No. 33740	0.4 mL/6 pk/adult (KIS1) - Advantage IGR 9
			11556	OWN	Report No. 33741	0.23 mL/4 pk/child (KIS1) - Advantage IGR 5
			11556	OWN	Report No. 33742	0.23 mL/4 pk/adult (KIS1) - Advantage IGR 5

Signature 	Douglas A. Spilker Manager, EPA Regulatory Affairs	November 24, 2009
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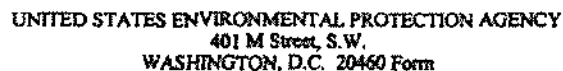
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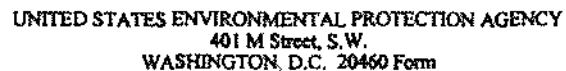
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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
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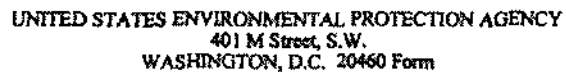
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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
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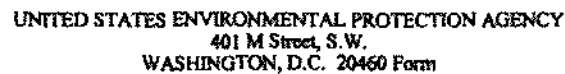
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DATA MATRIX

Date: November 24, 2009		EPA Reg No./File Symbol: 11556-XXX, 11556-XXX 11556-XXX		Page 5 of 11	
Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390		Product: Advantage® IGR 5 Advantage® IGR 9 Advantage® IGR 18		Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1	
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number Description

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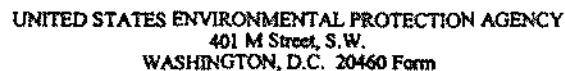
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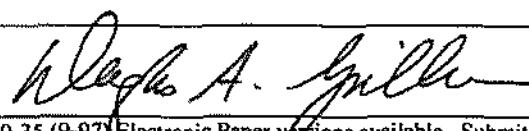
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Signature 	Douglas A. Spilker Manager, EPA Regulatory Affairs	November 24, 2009
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